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CHEMICAL COMPOUNDS

The present invention relates to heterocyclic derivatives having pharmaceutical activity, to processes for preparing such derivatives, to pharmaceutical compositions comprising such derivatives and to the use of such derivatives as active therapeutic agents.

Pharmaceutically active piperidine derivatives are disclosed in WO01/87839, EP-A1-1013276, WO00/08013, WO99/38514, WO99/04794, WO00/76511, WO00/76512, WO00/76513, WO00/76514, WO00/76972 and US 2002/0094989.

Chemokines are chemotactic cytokines that are released by a wide variety of cells to attract macrophages, T cells, eosinophils, basophils and neutrophils to sites of inflammation and also play a rôle in the maturation of cells of the immune system. Chemokines play an important rôle in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. These small secreted molecules are a growing superfamily of 8-14 kDa proteins characterised by a conserved four cysteine motif. The chemokine superfamily can be divided into two main groups exhibiting characteristic structural motifs, the Cys-X-Cys (C-X-C, or α) and Cys-Cys (C-C, or β) families. These are distinguished on the basis of a single amino acid insertion between the NH-proximal pair of cysteine residues and sequence similarity.

The C-X-C chemokines include several potent chemoattractants and activators of neutrophils such as interleukin-8 (IL-8) and neutrophil-activating peptide 2 (NAP-2).

The C-C chemokines include potent chemoattractants of monocytes and lymphocytes but not neutrophils such as human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2 and MCP-3), RANTES (Regulated on Activation, Normal T Expressed and Secreted), eotaxin and the macrophage inflammatory proteins 1α and 1β (MIP-1α and MIP-1β).

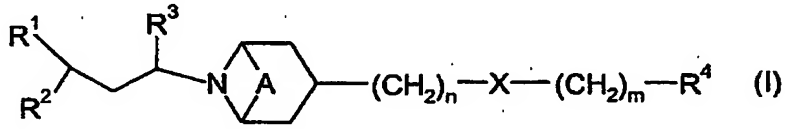
Studies have demonstrated that the actions of the chemokines are mediated by subfamilies of G protein-coupled receptors, among which are the receptors designated CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR1, CXCR2, CXCR3 and CXCR4. These receptors represent good targets for drug development since agents which modulate these receptors would be useful in the treatment of disorders and diseases such as those mentioned above.

The CCR5 receptor is expressed on T-lymphocytes, monocytes, macrophages, dendritic cells, microglia and other cell types. These detect and respond to several chemokines, principally "regulated on activation normal T-cell expressed and secreted" (RANTES), macrophage inflammatory proteins (MIP) MIP-1α and MIP-1β and monocyte chemoattractant protein-2 (MCP-2).

This results in the recruitment of cells of the immune system to sites of disease. In many diseases it is the cells expressing CCR5 which contribute, directly or indirectly, to tissue damage. Consequently, inhibiting the recruitment of these cells is beneficial in a wide range of diseases.

CCR5 is also a co-receptor for HIV-1 and other viruses, allowing these viruses to enter cells. Blocking the receptor with a CCR5 antagonist or inducing receptor internalisation with a CCR5 agonist protects cells from viral infection.

The present invention provides a compound of formula (I):



(I)

wherein:

A is absent or is $(CH_2)_2$;

R^1 is C_{1-8} alkyl, $C(O)NR^{10}R^{11}$, $C(O)_2R^{12}$, $NR^{13}C(O)R^{14}$, $NR^{15}C(O)NR^{16}R^{17}$, $NR^{18}C(O)_2R^{19}$, heterocyclyl (for example piperidine, piperazine, pyrrolidine or azetidine), aryl or heteroaryl;

R^{10}, R^{13}, R^{15}, R^{16} and R^{18} are hydrogen or C_{1-6} alkyl;

R^{11}, R^{12}, R^{14}, R^{17} and R^{19} are C_{1-8} alkyl (optionally substituted by halo, hydroxy, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl (optionally substituted by halo), C_{5-6} cycloalkenyl, $S(C_{1-4}$ alkyl), $S(O)(C_{1-4}$ alkyl), $S(O)_2(C_{1-4}$ alkyl), heteroaryl, aryl, heteroaryloxy or aryloxy), aryl, heteroaryl, C_{3-7} cycloalkyl (optionally substituted by halo or C_{1-4} alkyl), C_{4-7} cycloalkyl fused to a phenyl ring, C_{5-7} cycloalkenyl, or, heterocyclyl (itself optionally substituted by oxo, $C(O)(C_{1-6}$ alkyl), $S(O)_k(C_{1-6}$ alkyl), halo or C_{1-4} alkyl); or R^{11}, R^{12}, R^{14} and R^{17} can also be hydrogen;

or R^{10} and R^{11}, and/or R^{16} and R^{17} may join to form a 4-, 5- or 6-membered ring which optionally includes a nitrogen, oxygen or sulphur atom, said ring being optionally substituted by C_{1-6} alkyl, $S(O)_l(C_{1-6}$ alkyl) or $C(O)(C_{1-6}$ alkyl);

R^2 C_{1-6} alkyl, phenyl, heteroaryl or C_{3-7} cycloalkyl;

R^3 H or C_{1-4} alkyl;

R^4 is aryl or heteroaryl;

X is O or $S(O)_p$;

m and n are, independently, 0, 1, 2 or 3, provided m + n is 1 or more, and provided that when X is O then m and n are not both 1;

unless specified otherwise aryl, phenyl and heteroaryl moieties are independently optionally substituted by one or more of halo, cyano, nitro, hydroxy, $OC(O)NR^{20}R^{21}$, $NR^{22}R^{23}$, $NR^{24}C(O)R^{25}$, $NR^{26}C(O)NR^{27}R^{28}$, $S(O)_2NR^{29}R^{30}$, $NR^{31}S(O)_2R^{32}$, $C(O)NR^{33}R^{34}$, CO_2R^{36}, $NR^{37}CO_2R^{38}$, $S(O)_qR^{39}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy(C_{1-6})alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, phenyl, phenyl(C_{1-4})alkyl, phenoxy, phenylthio, phenylS(O), phenyl$S(O)_2$, phenyl(C_{1-4})alkoxy, heteroaryl, heteroaryl(C_{1-4})alkyl, heteroaryloxy or heteroaryl(C_{1-4})alkoxy; wherein any of the immediately foregoing phenyl and heteroaryl moieties are optionally substituted with halo, hydroxy, nitro, S(C_{1-4} alkyl), S(O)(C_{1-4} alkyl), $S(O)_2$(C_{1-4} alkyl), $S(O)_2NH_2$, $S(O)_2NH$(C_{1-4} alkyl), $S(O)_2N$(C_{1-4} alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, C(O)NH(C_{1-4} alkyl), C(O)N(C_{1-4} alkyl)$_2$, CO_2H, CO_2(C_{1-4} alkyl), NHC(O)(C_{1-4} alkyl), $NHS(O)_2$(C_{1-4} alkyl), CF_3 or OCF_3;

unless otherwise stated heterocyclyl is optionally substituted by C_{1-6} alkyl [optionally substituted by phenyl {which itself optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, cyano, nitro, CF_3, OCF_3, (C_{1-4} alkyl)C(O)NH, $S(O)_2NH_2$, C_{1-4} alkylthio, S(O)(C_{1-4} alkyl) or $S(O)_2$(C_{1-4} alkyl)} or heteroaryl {which itself optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, cyano, nitro, CF_3, (C_{1-4} alkyl)C(O)NH, $S(O)_2NH_2$, C_{1-4} alkylthio, S(O)(C_{1-4} alkyl) or $S(O)_2$(C_{1-4} alkyl)}], phenyl {optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, cyano, nitro, CF_3, OCF_3, (C_{1-4} alkyl)C(O)NH, $S(O)_2NH_2$, C_{1-4} alkylthio, S(O)(C_{1-4} alkyl) or $S(O)_2$(C_{1-4} alkyl)}, heteroaryl {optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, cyano, nitro, CF_3, (C_{1-4} alkyl)C(O)NH, $S(O)_2NH_2$, C_{1-4} alkylthio, S(O)(C_{1-4} alkyl) or $S(O)_2$(C_{1-4} alkyl)}, $S(O)_2NR^{40}R^{41}$, $C(O)R^{42}$, $C(O)_2$(C_{1-6} alkyl) (such as tert-butoxycarbonyl), $C(O)_2$(phenyl(C_{1-2} alkyl)) (such as benzyloxycarbonyl), $C(O)NHR^{43}$, $S(O)_2R^{44}$, $NHS(O)_2NHR^{45}$, $NHC(O)R^{46}$, $NHC(O)NHR^{47}$ or $NHS(O)_2R^{48}$, provided none of these last four substituents is linked to a ring nitrogen;

k, l, p and q are, independently, 0, 1 or 2;

R^{20}, R^{22}, R^{24}, R^{26}, R^{27}, R^{29}, R^{31}, R^{33}, R^{37} and R^{40} are, independently, hydrogen or C_{1-6} alkyl;

R^{21}, R^{23}, R^{25}, R^{28}, R^{30}, R^{32}, R^{34}, R^{36}, R^{38}, R^{39}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, R^{47} and R^{48} are, independently, C_{1-6} alkyl (optionally substituted by halo, hydroxy, C_{1-6} alkoxy, C_{1-6}

haloalkoxy, C_{3-6} cycloalkyl, C_{5-6} cycloalkenyl, $S(C_{1-4}$ alkyl), $S(O)(C_{1-4}$ alkyl), $S(O)_2(C_{1-4}$ alkyl), heteroaryl, phenyl, heteroaryloxy or phenyloxy), C_{3-7} cycloalkyl, phenyl or heteroaryl; wherein any of the immediately foregoing phenyl and heteroaryl moieties are optionally substituted with halo, hydroxy, nitro, $S(C_{1-4}$ alkyl), $S(O)(C_{1-4}$ alkyl), $S(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl$)_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl$)_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3;
R^{21}, R^{23}, R^{25}, R^{28}, R^{30}, R^{34}, R^{35}, R^{36}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46} and R^{47} may additionally be hydrogen;
or a pharmaceutically acceptable salt thereof or a solvate thereof.

Certain compounds of the present invention can exist in different isomeric forms (such as enantiomers, diastereomers, geometric isomers or tautomers). The present invention covers all such isomers and mixtures thereof in all proportions.

Suitable salts include acid addition salts such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate.

The compounds of the invention may exist as solvates (such as hydrates) and the present invention covers all such solvates.

Alkyl groups and moieties are straight or branched chain and, for example, comprise one to six (such as one to four) carbon atoms. Alkyl is, for example, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl or tert-butyl. Methyl is sometimes abbreviated to Me hereinbelow.

Fluoroalkyl includes, for example, one to six, such as one to three, fluorine atoms, and comprises, for example, a CF_3 group. Fluoroalkyl is, for example, CF_3 or CH_2CF_3.

Cycloalkyl is, for example, cyclopropyl, cyclopentyl or cyclohexyl.

Heterocyclyl is, for example, piperidine, piperazine, pyrrolidine, azetidine, tetrahydrofuran, morpholine or thiomorpholine.

Aryl includes phenyl and naphthyl. In one aspect of the invention aryl is phenyl.

Heteroaryl is, for example, an aromatic 5 or 6 membered ring, optionally fused to one or more other rings, comprising at least one heteroatom selected from the group comprising nitrogen, oxygen and sulphur; or an N-oxide thereof, or an S-oxide or S-dioxide thereof. Heteroaryl is, for example, furyl, thienyl (also known as thiophenyl), pyrrolyl, thiazolyl, isothiazolyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, [1,2,4]-triazolyl, pyridinyl,

pyrimidinyl, pyrazinyl, indolyl, benzo[b]furyl (also known as benzfuryl), benz[b]thienyl (also known as benzthienyl or benzthiophenyl), indazolyl, benzimidazolyl, benztriazolyl, benzoxazolyl, benzthiazolyl, 1,2,3-benzothiadiazolyl, an imidazopyridinyl (such as imidazo[1,2a]pyridinyl), thieno[3,2-b]pyridin-6-yl, 1,2,3-benzoxadiazolyl (also known as benzo[1,2,3]thiadiazolyl), 2,1,3-benzothiadiazolyl, benzofurazan (also known as 2,1,3-benzoxadiazolyl), quinoxalinyl, a pyrazolopyridine (for example 1H-pyrazolo[3,4-b]pyridinyl), quinolinyl, isoquinolinyl, a naphthyridinyl (for example [1,6]naphthyridinyl or [1,8]naphthyridinyl), a benzothiazinyl or dibenzothiophenyl (also known as dibenzothienyl); or an N-oxide thereof, or an S-oxide or S-dioxide thereof.

Aryloxy includes phenoxy.

Heteroaryloxy includes pyridinyloxy and pyrimidinyloxy.

Phenyl(C_{1-4} alkyl)alkyl is, for example, benzyl, 1-(phenyl)eth-1-yl or 1-(phenyl)eth-2-yl.

Heteroaryl(C_{1-4} alkyl)alkyl is, for example, pyridinylmethyl, pyrimidinylmethyl or 1-(pyridinyl)eth-2-yl.

Phenyl(C_{1-4} alkoxy) is, for example, benzyloxy or phenyl$CH(CH_3)O$.

Heteroaryl(C_{1-4} alkoxy) is, for example, pyridinylCH_2O, pyrimidinylCH_2O or pyridinyl$CH(CH_3)O$.

In one particular aspect the present invention provides a compound of formula (I) wherein, unless specified otherwise aryl, phenyl and heteroaryl moieties are independently optionally substituted by one or more of halo, hydroxy, nitro, S(C_{1-6} alkyl), S(O)(C_{1-6} alkyl), $S(O)_2$(C_{1-6} alkyl), $S(O)_2NH_2$, $S(O)_2NH$(C_{1-6} alkyl), $S(O)_2N$(C_{1-6} alkyl)$_2$, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, NH_2, NH(C_{1-6} alkyl), N(C_{1-6} alkyl)$_2$, $C(O)NH_2$, C(O)NH(C_{1-6} alkyl), C(O)N(C_{1-6} alkyl)$_2$, C(O)[N-linked heterocyclyl], CO_2H, CO_2(C_{1-6} alkyl), NHC(O)(C_{1-6} alkyl), NHC(O)O(C_{1-6} alkyl), $NHS(O)_2$(C_{1-6} alkyl), CF_3, CHF_2, CH_2F, CH_2CF_3, OCF_3, phenyl, heteroaryl, phenyl(C_{1-4} alkyl), heteroaryl(C_{1-4} alkyl), NHC(O)phenyl, NHC(O)heteroaryl, NHC(O)(C_{1-4} alkyl)phenyl, NHC(O)(C_{1-4} alkyl)heteroaryl, $NHS(O)_2$phenyl, $NHS(O)_2$heteroaryl, $NHS(O)_2$(C_{1-4} alkyl)phenyl, $NHS(O)_2$(C_{1-4} alkyl)heteroaryl, NHC(O)NH(C_{1-6} alkyl), NHC(O)NH(C_{3-7} cycloalkyl), NHC(O)NHphenyl, NHC(O)NHheteroaryl, NHC(O)NH(C_{1-4} alkyl)phenyl or NHC(O)NH(C_{1-4} alkyl)heteroaryl; wherein the foregoing phenyl and heteroaryl groups are optionally substituted by halo, hydroxy, nitro, S(C_{1-4} alkyl), S(O)(C_{1-4} alkyl), $S(O)_2$(C_{1-4} alkyl), $S(O)_2NH_2$, $S(O)_2NH$(C_{1-4} alkyl), $S(O)_2N$(C_{1-4} alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, C(O)NH(C_{1-4} alkyl),

$C(O)N(C_{1-4}$ alkyl$)_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), CF_3 or OCF_3.

In another aspect the present invention provides a compound of formula (I) wherein, unless specified otherwise aryl, phenyl and heteroaryl moieties are independently optionally substituted by one or more of halo, hydroxy, nitro, $S(C_{1-4}$ alkyl), $S(O)(C_{1-4}$ alkyl), $S(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl$)_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), CF_3, CHF_2, CH_2F, CH_2CF_3 or OCF_3.

In a further aspect of the invention heteroaryl is pyrrolyl, thienyl, imidazolyl, thiazolyl, isoxazolyl, pyridinyl, pyrimidinyl, pyrazinyl or quinolinyl.

In another aspect of the invention R^{10}, R^{13}, R^{15}, R^{16} and R^{18} are hydrogen or C_{1-4} alkyl (for example methyl). In yet another aspect R^{10}, R^{13}, R^{15}, R^{16} and R^{18} are hydrogen.

In a further aspect of the invention R^{11}, R^{12}, R^{14}, R^{17}, R^{18} and R^{19} are C_{1-8} alkyl (optionally substituted by halo, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl (optionally substituted by halo), C_{5-6} cycloalkenyl, $S(O)_2(C_{1-4}$ alkyl), heteroaryl, phenyl, heteroaryloxy or aryloxy), phenyl, heteroaryl, C_{3-7} cycloalkyl (optionally substituted by halo or C_{1-4} alkyl), C_{4-7} cycloalkyl fused to a phenyl ring, C_{5-7} cycloalkenyl, or, heterocyclyl (itself optionally substituted by oxo, $C(O)(C_{1-6}$ alkyl), $S(O)_k(C_{1-4}$ alkyl), halo or C_{1-4} alkyl); k is 0, 1 or 2; or R^{10} and R^{11}, and/or R^{16} and R^{17} may join to form a 4-, 5- or 6-membered ring which optionally includes a nitrogen, oxygen or sulphur atom, said ring being optionally substituted by C_{1-6} alkyl or $C(O)(C_{1-6}$ alkyl).

In yet another aspect of the invention R^{11}, R^{12}, R^{14}, R^{17} and R^{19} are C_{1-8} alkyl (optionally substituted by halo (such as fluoro)), phenyl (optionally substituted as recited above), C_{3-6} cycloalkyl (optionally substituted by halo (such as fluoro)) or C-linked nitrogen containing heterocyclyl (optionally substituted on the ring nitrogen).

In another aspect of the invention R^1 is $NR^{13}C(O)R^{14}$, wherein R^{13} and R^{14} are as defined above.

In yet another aspect of the invention R^{14} is C_{1-8} alkyl (optionally substituted by halo (such as fluoro, for example to form CF_3CH_2)), phenyl (optionally substituted as recited above), C_{3-6} cycloalkyl (optionally substituted by halo (such as fluoro, for example to form 1,1-difluorocyclohex-4-yl)) or C-linked nitrogen containing heterocyclyl (such as pyran or piperidine, optionally substituted on the ring nitrogen).

In a further aspect of the invention heterocyclyl is optionally substituted (such as singly substituted for example on a ring nitrogen atom when present) by C_{1-6} alkyl [optionally substituted by phenyl {which itself optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, cyano, nitro, CF_3, OCF_3, (C_{1-4} alkyl)C(O)NH, $S(O)_2NH_2$, C_{1-4} alkylthio or $S(O)_2(C_{1-4}$ alkyl)} or heteroaryl {which itself optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, cyano, nitro, CF_3, (C_{1-4} alkyl)C(O)NH, $S(O)_2NH_2$, C_{1-4} alkylthio or $S(O)_2(C_{1-4}$ alkyl)}], phenyl {optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, cyano, nitro, CF_3, OCF_3, (C_{1-4} alkyl)C(O)NH, $S(O)_2NH_2$, C_{1-4} alkylthio or $S(O)_2(C_{1-4}$ alkyl)}, heteroaryl {optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, cyano, nitro, CF_3, (C_{1-4} alkyl)C(O)NH, $S(O)_2NH_2$, C_{1-4} alkylthio or $S(O)_2(C_{1-4}$ alkyl)}, $S(O)_2NR^{40}R^{41}$, $C(O)R^{42}$, $C(O)NHR^{43}$ or $S(O)_2R^{44}$; wherein R^{40}, R^{41}, R^{42}, R^{43} and R^{44} are, independently, hydrogen or C_{1-6} alkyl.

In yet another aspect of the invention R^1 is optionally substituted aryl (such as optionally substituted phenyl) or optionally substituted heteroaryl, wherein the optional substituents are as recited above.

In a further aspect of the invention R^1 is optionally substituted heterocyclyl, such as optionally substituted: piperidin-1-yl, piperidin-4-yl, piperazin-1-yl, pyrrolidin-1-yl, pyrrolidin-3-yl, azetidin-1-yl or azetidin-3-yl.

In a still further aspect of the invention the heterocyclyl of R^1 is mono-substituted by C_{1-6} alkyl, C_{3-7} cycloalkyl, phenyl {optionally substituted by halo (for example fluoro), C_{1-4} alkyl (for example methyl), C_{1-4} alkoxy (for example methoxy), CF_3 or OCF_3}, $S(O)_2(C_{1-4}$ alkyl) (for example $S(O)_2CH_3$, $S(O)_2CH_2CH_3$ or $S(O)_2CH(CH_3)_2$), $S(O)_2(C_{1-4}$ fluoroalkyl) (for example $S(O)_2CF_3$ or $S(O)_2CH_2CF_3$), $S(O)_2$phenyl {optionally substituted (such as mono-substituted) by halo (for example chloro), cyano, C_{1-4} alkyl, C_{1-4} alkoxy, CF_3, OCF_3, $S(O)_2(C_{1-4}$ alkyl) (for example $S(O)_2CH_3$ or $S(O)_2CH_2CH_2CH_3$) or $S(O)_2(C_{1-4}$ fluoroalkyl) (for example $S(O)_2CH_2CF_3$)}, benzyl {optionally substituted by halo (for example chloro or fluoro), C_{1-4} alkyl, C_{1-4} alkoxy (for example methoxy), CF_3 or OCF_3}, C(O)H, C(O)(C_{1-4} alkyl), benzoyl {optionally substituted by halo (for example chloro or fluoro), C_{1-4} alkyl (for example methyl), C_{1-4} alkoxy, CF_3 or OCF_3}, $C(O)_2(C_{1-4}$ alkyl), $C(O)NH_2$, C(O)NH(C_{1-4} alkyl) or C(O)NHphenyl {optionally substituted by halo (for example fluoro), C_{1-4} alkyl, C_{1-4} alkoxy, CF_3 or OCF_3}. In a still further aspect when said heterocyclyl is a 4-substituted piperidin-1-yl, a 1-substituted piperidin-4-yl, a 1-substituted piperazin-1-yl, a 3-substituted pyrrolidin-1-yl, a 1-substituted pyrrolidin-3-yl, a 3-substituted azetidin-1-yl or a 1-substituted azetidin-3-yl.

In yet another aspect of the invention R^2 is phenyl or heteroaryl, either of which is optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, $S(O)_n(C_{1-4}$ alkyl), nitro, cyano or CF_3; wherein n is 0, 1 or 2, for example 0 or 2.

In a still further aspect R^2 is optionally substituted (for example unsubstituted or substituted in the 2-, 3-, or 3- and 5- positions) phenyl (such as optionally substituted by halo (such as chloro or fluoro), cyano, methyl, ethyl, methoxy, ethoxy or CF_3), or optionally substituted (for example unsubstituted or mono-substituted) heteroaryl (such as optionally substituted by halo (such as chloro or fluoro), cyano, methyl, ethyl, methoxy, ethoxy or CF_3).

In another aspect R^2 is optionally substituted (for example unsubstituted or substituted in the 2-, 3-, or 3- and 5- positions) phenyl (such as optionally substituted by halo (for example chloro or fluoro)). For example R^2 is phenyl, 3-fluorophenyl, 3-chlorophenyl, 3,5-difluorophenyl.

In yet another aspect of the invention R^3 is hydrogen or methyl. In a further aspect of the invention when R^3 is C_{1-4} alkyl (such as methyl) the carbon to which R^3 is attached has the R absolute configuration. In yet another aspect of the invention R^3 is hydrogen.

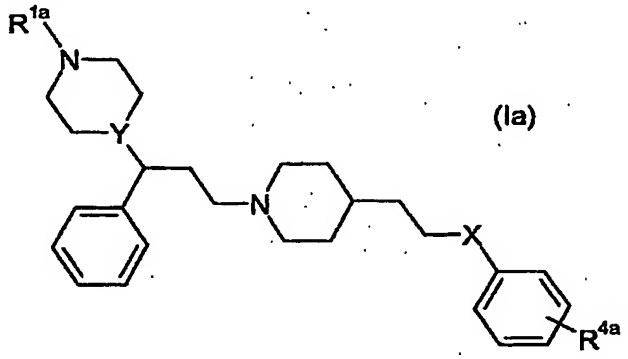
In a still further aspect the present invention provides a compound of the invention wherein R^4 is optionally substituted phenyl.

In a still further aspect of the invention A is absent.

In another aspect X is O or $S(O)_2$. In yet another aspect X is $S(O)_2$.

In a further aspect of the invention m is 2 and n is 0 or n is 2 and m is 0.

In a still further aspect the present invention provides a compound of formula (Ia):

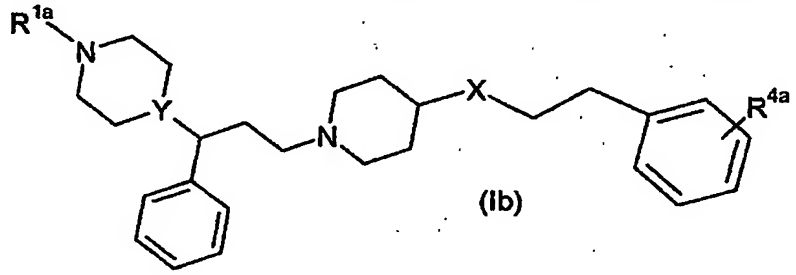


(Ia)

wherein X is as defined above; Y is CH or N; R^{4a} is as defined for optional substituents on optionally substituted phenyl (above); and R^{1a} is mono-substituted by C_{1-6} alkyl, C_{3-7} cycloalkyl, phenyl {optionally substituted by halo (for example fluoro), C_{1-4} alkyl (for example methyl), C_{1-4} alkoxy (for example methoxy), CF_3 or OCF_3}, $S(O)_2(C_{1-4}$ alkyl) (for

example $S(O)_2CH_3$, $S(O)_2CH_2CH_3$ or $S(O)_2CH(CH_3)_2$), $S(O)_2$(C_{1-4} fluoroalkyl) (for example $S(O)_2CF_3$ or $S(O)_2CH_2CF_3$), $S(O)_2$phenyl {optionally substituted (such as mono-substituted) by halo (for example chloro), cyano, C_{1-4} alkyl, C_{1-4} alkoxy, CF_3, OCF_3, $S(O)_2$(C_{1-4} alkyl) (for example $S(O)_2CH_3$ or $S(O)_2CH_2CH_2CH_3$) or $S(O)_2$(C_{1-4} fluoroalkyl) (for example $S(O)_2CH_2CF_3$)}, benzyl {optionally substituted by halo (for example chloro or fluoro), C_{1-4} alkyl, C_{1-4} alkoxy (for example methoxy), CF_3 or OCF_3}, C(O)H, C(O)(C_{1-4} alkyl), benzoyl {optionally substituted by halo (for example chloro or fluoro), C_{1-4} alkyl (for example methyl), C_{1-4} alkoxy, CF_3 or OCF_3}, $C(O)_2$(C_{1-4} alkyl), $C(O)NH_2$, C(O)NH(C_{1-4} alkyl) or C(O)NHphenyl {optionally substituted by halo (for example fluoro), C_{1-4} alkyl, C_{1-4} alkoxy, CF_3 or OCF_3}.

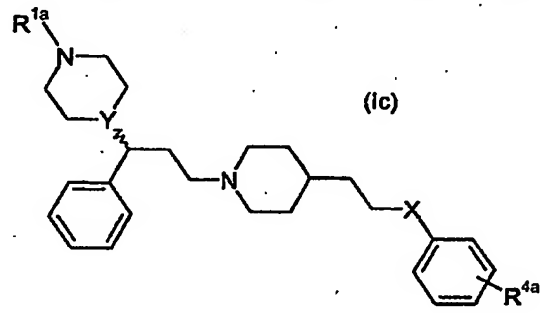
In another aspect the present invention provides a compound of formula (Ib):



(Ib)

wherein X, Y, R^{1a} and R^{4a} are as defined above.

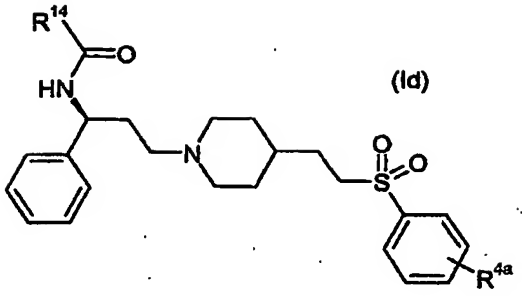
In yet another aspect the present invention provides a compound of formula (Ic):



(Ic)

wherein X, Y, R^{1a} and R^{4a} are as defined above.

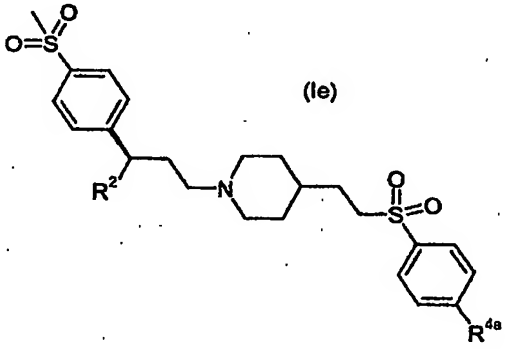
In a further aspect the present invention provides a compound of formula (Id):



(Id)

wherein R^{14} and R^{4a} are as defined above.

In a still further aspect the present invention provides a compound of formula (Ie):



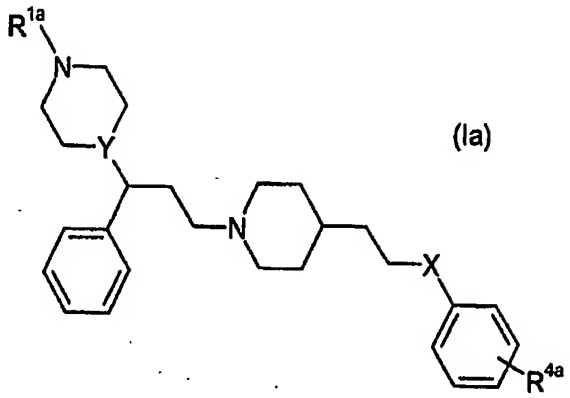
(Ie)

wherein R^2 and R^{4a} are as defined above.

The compounds listed in Tables I to V illustrate the invention.

Table I

Table I comprises compounds of formula (Ia)



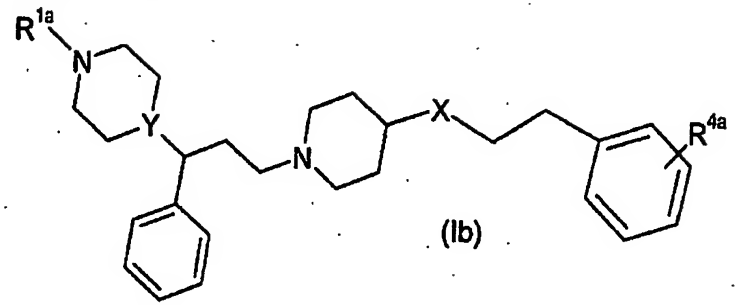
(Ia)

Compound No	Y	R^{1a}	X	R^{4a}	MS (MH+)
1	CH	ethanesulphonyl	O	H	499
2	N	benzenesulphonyl	O	H	548
3	N	benzenesulphonyl	O	4-methanesulphonyl	626
4	N	ethanesulphonyl	O	4-methanesulphonyl	578
5	N	benzenesulphonyl	$S(O)_2$	4-methanesulphonyl	674
6	N	methanesulphonyl	S	4-methylthio	562
7	N	ethanesulphonyl	S	4-methylthio	548
8	N	phenyl	$S(O)_2$	4-methanesulphonyl	610
9	N	methanesulphonyl	$S(O)_2$	4-methanesulphonyl	612
10	N	ethanesulphonyl	$S(O)_2$	4-methanesulphonyl	626

11	CH	methanesulphonyl	$S(O)_2$	4-fluoro	551
12	N	phenyl	$S(O)_2$	4-fluoro	550
13	CH	methanesulphonyl	$S(O)_2$	4-methanesulphonyl	611
14	CH	methanesulphonyl	$S(O)_2$	4-chloro	567
15	CH	trifluoromethanesulphonyl	$S(O)_2$	4-chloro	621
16	CH	methanesulphonyl	$S(O)_2$	Hydrogen	533
17	CH	methanesulphonyl	$S(O)_2$	4-methyl	547
18	CH	methanesulphonyl	$S(O)_2$	4-trifluoromethyl	601
19	CH	methanesulphonyl	$S(O)_2$	4-methoxy	563

Table II

Table II comprises compounds of formula (Ib)



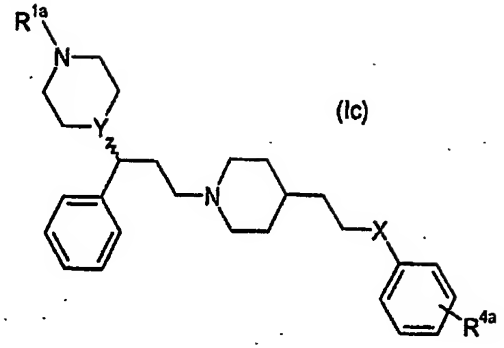
(Ib)

Compound No	R^{1a}	Y	X	m	R^{4a}	MS (MH+)
1	benzenesulphonyl	N	$S(O)_2$	2	4-methanesulphonyl	674

2	phenyl	N	$S(O)_2$	2	4-methanesulphonyl	610

Table III

Table III comprises compounds of formula (Ic)



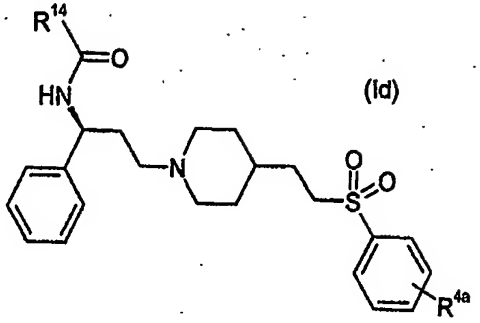
(Ic)

Compound No	R^{1a}	Y	Stereochemistry	X	R^{4a}	MS (MH+)
1	phenyl	N	R or S	$S(O)_2$	4-methanesulphonyl	610
2	phenyl	N	S or R	$S(O)_2$	4-methanesulphonyl	610
3	methanesulphonyl	CH	R or S	$S(O)_2$	4-fluoro	551
4	methanesulphonyl	CH	S or R	$S(O)_2$	4-fluoro	551
5	methanesulphonyl	N	S or R	$S(O)_2$	hydrogen	534
6	phenylsulphonyl	N	S or R	$S(O)_2$	hydrogen	596
7	methanesulphonyl	N	S or R	$S(O)_2$	4-methoxy	564
8	trifluoromethane-sulphonyl	N	S or R	$S(O)_2$	4-methoxy	618
9	methanesulphonyl	N	S or R	$S(O)_2$	4-trifluoromethyl	602

10	methanesulphonyl	N	S or R	$S(O)_2$	4-methyl	548
11	trifluoromethane-sulphonyl	N	S or R	$S(O)_2$	4-methyl	602
12	trifluoromethane-sulphonyl	N	S or R	$S(O)_2$	4-trifluoromethyl	656
13	trifluoromethane-sulphonyl	N	S or R	$S(O)_2$	hydrogen	588
14	methanesulphonyl	N	S or R	$S(O)_2$	4-fluoro	552
15	methanesulphonyl	N	S or R	$S(O)_2$	4-chloro	568
16	phenylsulphonyl	N	S or R	$S(O)_2$	4-trifluoromethyl	664
17	trifluoromethane-sulphonyl	N	S or R	$S(O)_2$	4-fluoro	606
18	trifluoromethane-sulphonyl	N	S or R	$S(O)_2$	4-chloro	622
19	methanesulphonyl	N	S or R	$S(O)_2$	4-methanesulphonyl	612
20	trifluoromethane-sulphonyl	N	S or R	$S(O)_2$	4-methanesulphonyl	666

Table IV

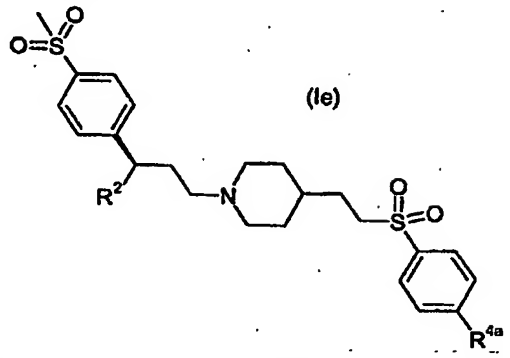
Table IV comprises compounds of formula (Id)



Compound No	R^{14}	Stereochemistry	R^{4a}	MS (MH+)
1	2,2,2-trifluoropropionyl	S	4-methanesulphonyl	575
2	4-chlorobenzoyl	S	4-methanesulphonyl	603

Table V

Table V comprises compounds of formula (Ie)



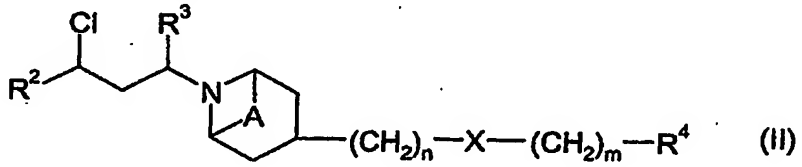
(Ie)

Compound No.	R^2	R^{4a}	MS (MH+)
1	2-thienyl	4-methanesulphonyl	610
2	3-thienyl	4-methanesulphonyl	610
3	phenyl	4-methanesulphonyl	604
4	phenyl	4-fluoro	544
5	5-chloro-2-thienyl	4-methanesulphonyl	645
6	4-chloro-2-thienyl	4-methanesulphonyl	645
7	3,5-difluorophenyl	4-methanesulphonyl	640
8	3,5-difluorophenyl	4-fluoro	580
9	3,5-difluorophenyl	hydrogen	562
10	3,5-difluorophenyl	4-methoxy	592

In yet another aspect the invention provides each individual compound listed in the tables above.

The compounds of formula (I), (Ia), (Ib), (Ic), (Id) and (Ie) can be prepared as shown below.

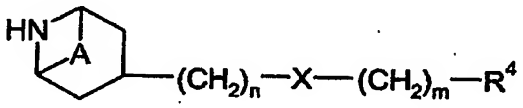
A compound of the invention wherein R^1 is an N-linked optionally substituted heterocycle can be prepared by reacting a compound of formula (II):



(II)

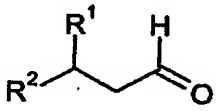
wherein R^2, R^3, R^4, m, n, A and X are as defined above, with a compound R^1H (wherein the H is on a heterocycle ring nitrogen atom) wherein R^1 is as defined above, in the presence of a suitable base (for example a tri(C_{1-6} alkyl)amine such as triethylamine or Hunig's base), in a suitable solvent (such as a chlorinated solvent, for example dichloromethane) and, for example, at a room temperature (for example 10-30°C), optionally in the presence of sodium iodide.

A compound of the invention, wherein R^3 is hydrogen, can be prepared by coupling a compound of formula (III):



(III)

wherein R^4, m, n, A and X are as defined above, with a compound of formula (IV):



(IV)

wherein R^1 and R^2 are as defined above, in the presence of $NaBH(OAc)_3$ (wherein Ac is $C(O)CH_3$) in a suitable solvent (such as a chlorinated solvent, for example dichloromethane) at room temperature (for example 10-30°C).

Alternatively, compounds of the invention can be prepared according to Schemes 1-7 (below).

Alternatively, compounds of the invention can be prepared by using or adapting methods described in WO01/87839, EP-A1-1013276, WO00/08013, WO99/38514, WO99/04794, WO00/76511, WO00/76512, WO00/76513, WO00/76514, WO00/76972 or US 2002/0094989.

The starting materials for these processes are either commercially available or can be prepared by literature methods, adapting literature methods or by following or adapting Methods herein described.

In a still further aspect the invention provides processes for preparing the compounds of formula (I), (Ia), (Ib), (Ic), (Id) and (Ie). Many of the intermediates in the processes are novel and these are provided as further features of the invention.

The compounds of the invention have activity as pharmaceuticals, in particular as modulators (such as agonists, partial agonists, inverse agonists or antagonists) of chemokine receptor (especially CCR5) activity, and may be used in the treatment of autoimmune,

inflammatory, proliferative or hyperproliferative diseases, or immunologically-mediated diseases (including rejection of transplanted organs or tissues and Acquired Immunodeficiency Syndrome (AIDS)).

The compounds of the present invention are also of value in inhibiting the entry of viruses (such as human immunodeficiency virus (HIV)) into target calls and, therefore, are of value in the prevention of infection by viruses (such as HIV), the treatment of infection by viruses (such as HIV) and the prevention and/or treatment of acquired immune deficiency syndrome (AIDS).

According to a further feature of the invention there is provided a compound of the formula (I), (Ia), (Ib), (Ic), (Id) or (Ie), or a pharmaceutically acceptable salt thereof or a solvate thereof, for use in a method of treatment of a warm blooded animal (such as man) by therapy (including prophylaxis).

According to a further feature of the present invention there is provided a method for modulating chemokine receptor activity (especially CCR5 receptor activity) in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof or a solvate thereof.

The present invention also provides the use of a compound of the formula (I), (Ia), (Ib), (Ic), (Id) or (Ie), or a pharmaceutically acceptable salt thereof or a solvate thereof, as a medicament, especially a medicament for the treatment of transplant rejection, respiratory disease, psoriasis or rheumatoid arthritis (especially rheumatoid arthritis). [Respiratory disease is, for example, COPD, asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)} or rhinitis {acute, allergic, atrophic rhinitis or chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis}; and is particularly asthma or rhinitis].

In another aspect the present invention provides the use of a compound of the formula (I), (Ia), (Ib), (Ic), (Id) or (Ie), or a pharmaceutically acceptable salt thereof or a solvate thereof, in the manufacture of a medicament for use in therapy (for example modulating chemokine receptor activity (especially CCR5 receptor activity (especially rheumatoid arthritis)) in a warm blooded animal, such as man).

The invention also provides a compound of the formula (I), (Ia), (Ib), (Ic), (Id) or (Ie), or a pharmaceutically acceptable salt thereof or a solvate thereof, for use as a medicament, especially a medicament for the treatment of rheumatoid arthritis.

In another aspect the present invention provides the use of a compound of the formula (I), (Ia), (Ib), (Ic), (Id) or (Ie), or a pharmaceutically acceptable salt thereof or a solvate thereof, in the manufacture of a medicament for use in therapy (for example modulating chemokine receptor activity (especially CCR5 receptor activity (especially rheumatoid arthritis)) in a warm blooded animal, such as man).

The invention further provides the use of a compound of formula (I), (Ia), (Ib), (Ic), (Id) or (Ie), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of:

(1) (the respiratory tract) obstructive diseases of airways including: chronic obstructive pulmonary disease (COPD) (such as irreversible COPD); asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)}; bronchitis {such as eosinophilic bronchitis}; acute, allergic, atrophic rhinitis or chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis; sarcoidosis; farmer's lung and related diseases; nasal polyposis; fibroid lung or idiopathic interstitial pneumonia;

(2) (bone and joints) arthrides including rheumatic, infectious, autoimmune, seronegative spondyloarthropathies (such as ankylosing spondylitis, psoriatic arthritis or Reiter's disease), Behçet's disease, Sjogren's syndrome or systemic sclerosis;

(3) (skin and eyes) psoriasis, atopic dermatitis, contact dermatitis or other eczmatous dermitides, seborrhoetic dermatitis, Lichen planus, Phemphigus, bullous Phemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides erythemas, cutaneous eosinophilias, uveitis, Alopecia areata or vernal conjunctivitis;

(4) (gastrointestinal tract) Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, irritable bowel disease or food-related allergies which have effects remote from the gut (for example migraine, rhinitis or eczema);

(5) (Allograft rejection) acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea; or chronic graft versus host disease; and/or

(6) (other tissues or diseases) Alzheimer's disease, multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), Lupus disorders (such as lupus erythematosus or systemic lupus), erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, leprosy (such as lepromatous leprosy), Peridontal disease, Sezary syndrome, idiopathic thrombocytopenia pupura or disorders of the menstrual cycle;

in a warm blooded animal, such as man.

The present invention further provides a method of treating a chemokine mediated disease state (especially a CCR5 mediated disease state) in a warm blooded animal, such as man, which comprises administering to a mammal in need of such treatment an effective amount of a compound of formula (I), (Ia), (Ib), (Ic), (Id) or (Ie), or a pharmaceutically acceptable salt thereof or solvate thereof.

In order to use a compound of the invention, or a pharmaceutically acceptable salt thereof or solvate thereof, for the therapeutic treatment of a warm blooded animal, such as man, in particular modulating chemokine receptor (for example CCR5 receptor) activity, said ingredient is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore in another aspect the present invention provides a pharmaceutical composition which comprises a compound of the formula (I), (Ia), (Ib), (Ic), (Id) or (Ie), or a pharmaceutically acceptable salt thereof or a solvate thereof (active ingredient), and a pharmaceutically acceptable adjuvant, diluent or carrier. In a further aspect the present invention provides a process for the preparation of said composition which comprises mixing active ingredient with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by topical (such as to the lung and/or airways or to the skin), oral, rectal or parenteral administration. For these

purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, aerosols, dry powder formulations, tablets, capsules, syrups, powders, granules, aqueous or oily solutions or suspensions, (lipid) emulsions, dispersible powders, suppositories, ointments, creams, drops and sterile injectable aqueous or oily solutions or suspensions.

A suitable pharmaceutical composition of this invention is one suitable for oral administration in unit dosage form, for example a tablet or capsule which contains between 0.1mg and 1g of active ingredient.

In another aspect a pharmaceutical composition of the invention is one suitable for intravenous, subcutaneous or intramuscular injection.

Each patient may receive, for example, an intravenous, subcutaneous or intramuscular dose of 0.01mgkg^{-1} to 100mgkg^{-1} of the compound, preferably in the range of 0.1mgkg^{-1} to 20mgkg^{-1} of this invention, the composition being administered 1 to 4 times per day. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively the intravenous dose may be given by continuous infusion over a period of time. Alternatively each patient will receive a daily oral dose which is approximately equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day.

The following illustrate representative pharmaceutical dosage forms containing the compound of formula (I), (Ia), (Ib), (Ic), (Id) or (Ie), or a pharmaceutically acceptable salt thereof or a solvent thereof (hereafter Compound X), for therapeutic or prophylactic use in humans:

(a)

Tablet I	mg/tablet
Compound X	100
Lactose Ph.Eur.	179
Croscarmellose sodium	12.0
Polyvinylpyrrolidone	6
Magnesium stearate	3.0

(b)

Tablet II	mg/tablet

Compound X	50
Lactose Ph.Eur.	229
Croscarmellose sodium	12.0
Polyvinylpyrrolidone	6
Magnesium stearate	3.0

(c)

Tablet III	mg/tablet
Compound X	1.0
Lactose Ph.Eur.	92
Croscarmellose sodium	4.0
Polyvinylpyrrolidone	2.0
Magnesium stearate	1.0

(d)

Capsule	mg/capsule
Compound X	10
Lactose Ph.Eur.	389
Croscarmellose sodium	100
Magnesium stearate	1.0

(e)

Injection I	(50 mg/ml)
Compound X	5.0% w/v
Isotonic aqueous solution	to 100%

Buffers, pharmaceutically-acceptable cosolvents such as polyethylene glycol, polypropylene glycol, glycerol or ethanol or complexing agents such as hydroxy-propyl β-cyclodextrin may be used to aid formulation.

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

The invention will now be illustrated by the following non-limiting Examples in which, unless stated otherwise:

(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25°C;

(ii) organic solutions were dried over anhydrous magnesium sulfate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30 mm Hg) with a bath temperature of up to 60°C;

(iii) chromatography unless otherwise stated means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates; where a "Bond Elut" column is referred to, this means a column containing 10g or 20g of silica of 40 micron particle size, the silica being contained in a 60ml disposable syringe and supported by a porous disc, obtained from Varian, Harbor City, California, USA under the name "Mega Bond Elut SI". Where an "Isolute™ SCX column" is referred to, this means a column containing benzenesulphonic acid (non-endcapped) obtained from International Sorbent Technology Ltd., 1st House, Duffryn Industial Estate, Ystrad Mynach, Hengoed, Mid Glamorgan, UK. Where "Argonaut™ PS-*tris*-amine scavenger resin" is referred to, this means a *tris*-(2-aminoethyl)amine polystyrene resin obtained from Argonaut Technologies Inc., 887 Industrial Road, Suite G, San Carlos, California, USA.

(iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;

(v) yields, when given, are for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;

(vi) when given, ^{1}H NMR data is quoted and is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300 MHz using perdeuterio DMSO (CD_3SOCD_3) as the solvent unless otherwise stated; coupling constants (J) are given in Hz;

(vii) chemical symbols have their usual meanings; SI units and symbols are used;

(viii) solvent ratios are given in percentage by volume;

(ix) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionisation (APCI) mode using a direct exposure probe; where indicated ionisation was effected by electrospray (ES); where values for m/z are given, generally only ions which

indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion - $(M+H)^+$;

(x) LCMS characterisation was performed using a pair of Gilson 306 pumps with Gilson 233 XL sampler and Waters ZMD4000 mass spectrometer. The LC comprised water symmetry 4.6x50 column C18 with 5 micron particle size. The eluents were: A, water with 0.05% formic acid and B, acetonitrile with 0.05% formic acid. The eluent gradient went from 95% A to 95% B in 6 minutes. Where indicated ionisation was effected by electrospray (ES); where values for m/z are given, generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion - $(M+H)^+$;

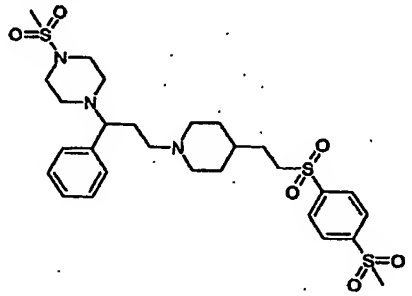
(xi) PS-NCO resin is an isocyanate resin and is available from Argonaut; and,

(xii) the following abbreviations are used:

THF	tetrahydrofuran;
Boc	tert-butoxycarbonyl

Example 1

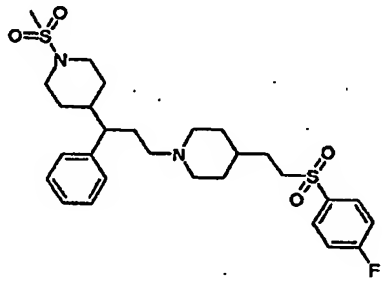
This Example illustrates the preparation of N-(3-phenyl-3-[4-methanesulphonylpiperazin-1-yl]propyl)-4-[2-(4-methanesulphonylphenylsulphonyl)ethyl]-piperidine (Compound No. 8, Table I).



N-(3-Phenyl-3-chloropropyl)-4-[2-(4-methanesulphonylphenylsulphonyl)ethyl]-piperidine (prepared according to Method D; 180mg) was added to a solution of N-methanesulphonylpiperazine (61mg) and triethylamine (0.102ml) in dichloromethane (10ml) and the mixture was allowed to stand at room temperature for 16 hours. The reaction mixture was poured onto a 20g silica Bond Elut eluted with a solvent gradient (ethyl acetate- 25% methanol/ethyl acetate). The title compound was obtained, yield 67mg, MH^+ 612. NMR ($CDCl_3$): 1,6-1.8 (m, 7H) 2.2-2.6(m, 9H) 2.7(m, 1H) 2.75 (s, 3H) 3.2 (m, 11H) 3.45 (m, 1H) 7.2 (d, 2H) 7.3 (m, 3H) 8.2 (m, 4H).

Example 2

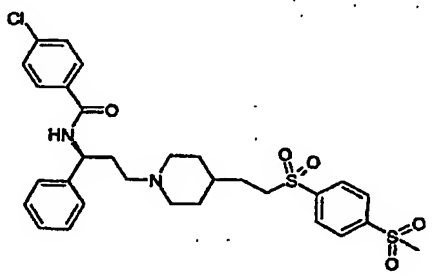
This Example illustrates the preparation of N-(3-phenyl-3-[1-methanesulphonyl-piperidin-4-yl]propyl)-4-[2-(4-fluorophenylsulphonyl)ethyl]piperidine. (Compound No. 10, Table I).



Sodium triacetoxyborohydride (267 mg) was added to a mixture of 2-(1-methanesulphonylpiperidin-4-yl)-2-phenylpropionaldehyde (247 mg) and 4-(2-[4-fluorophenylsulphonyl]ethyl)piperidine hydrochloride salt (288 mg) (CAS 313994-09-1) in dichloromethane (20 ml) and the mixture was stirred for 16 hours. The reaction mixture was washed successively with 2M sodium hydroxide (10 ml), water (10 ml) and brine (10 ml) and was dried. The residue obtained on removal of the solvent was chromatographed on a 20g silica Bond Elut column eluting with a solvent gradient (ethyl acetate-20% methanol/ethyl acetate) to give the title compound, yield 250mg, MH^+ 551. NMR ($CDCl_3$): 1.2 (m, 5H), 1.4 (m, 4H), 1.6-1.8 (m, 8H), 2.0 (m, 3H), 2.4 (m, 1H), 2.5-2.6 (m, 2H), 2.8 (s, 3H), 2.85 (m, 2H), 3.1 (m, 2H), 3.7 (d, 1 H), 3.85 (d, 1H), 7.1 (m, 2H), 7.3 (m, 5H), 7.9 (m, 2H).

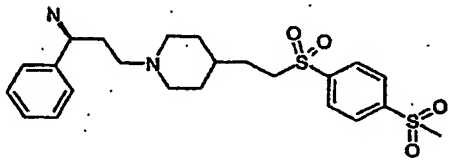
Example 3

This Example illustrates the preparation of (S) N-(3-phenyl-3-[4-chlorobenzoyl-amino]propyl-4-[2-(4-methanesulphonylphenylsulphonyl)ethyl]piperidine (Compound No. 2, Table IV).



4-Chlorobenzoyl chloride (76µl) was added to a solution of (S) N-(3-amino-3-phenylpropyl)-4-[2-(4-methanesulphonylphenylsulphonyl)ethyl]piperidine (280mg) and triethylamine (157µl) in dichloromethane (15ml) and the mixture was stirred for 1 hour then washed with water (15ml) and brine (15ml) and dried. Removal of the solvent gave the title compound as a white solid, yield 320mg, MH^+ 602. NMR (d6 DMSO): 1.0 (m, 2H), 1.2 (m, 1H), 1.5 (m, 2H), 1.6 (m, 2H), 1.8 (m, 2H), 1.9 (m, 2H), 2.25 (m, 2H), 2.8 (m, 2H), 3.3 (m,3H), 3.4 m, 2H), 5.0 (q, 1H), 7.2 (m, 1H), 7.3 (m,3H), 7.5 (d, 2H), 7.85 (d, 2H), 8.2 (m, 4H), 8.9 (d, 1H).

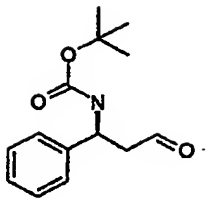
(S) N-(3-amino-3-phenylpropyl)-4-[2-(4-methanesulphonylphenylsulphonyl)ethyl]piperidine



Sodium triacetoxyborohydride (1.6g) was added to a mixture of (S) 3-phenyl-3-(tert. butoxycarbonylamino)propionaldehyde (1.23g) and 4-[2-(4-methanesulphonylphenyl-sulphonyl)ethyl]piperidine hydrochloride (1.215g) (Method B) in dichloromethane (50ml) and the mixture was stirred for 16 hours. The reaction mixture was washed successively with 2M sodium hydroxide (15ml), water (15ml) and brine (15ml) and dried. The dichloromethane solution was stirred with PS-NCO (isocyanate resin, 1.5g) for 16 hours and filtered. The filtrate was chromatographed on a 50g silica Bond Elut column eluting with ethyl acetate to give the Boc protected title compound as a white solid, yield 1.595g, MH^+ 565.

The Boc protected compound (1.59g) was dissolved in 4M HCl/dioxane (10ml) and allowed to stand at room temperature for 1 hour. The reaction mixture was evaporated to dryness, redissolved in 2M sodium hydroxide (10ml) and extracted with dichloromethane (2x20ml) and dried. Removal of the solvent gave the title compound, yield 0.56g, MH^+ 465.

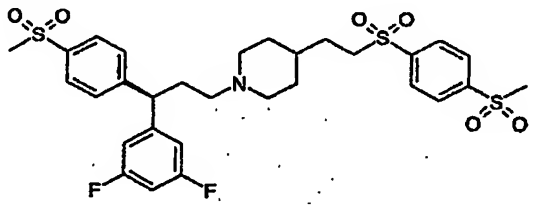
(S) 3-phenyl-3-(tert-butoxycarbonylamino)propionaldehyde



Lithium aluminium hydride (19 ml of 1M solution in THF) was added to a solution of (S) 3-phenyl-3-(tert-butoxycarbonylamino)propionic acid (5.01g) in THF (50ml) at 0°C. The reaction mixture was stirred for 1 hour and ethyl acetate (20ml) was added followed by water (0.5ml), 6M sodium hydroxide (0.5ml) and water (5ml). The mixture was filtered through Celite and evaporated to dryness to give (S) 3-phenyl-3-(tert-butoxycarbonylamino)propanol, yield 2.89g. This material was dissolved in dichloromethane (40ml) and Dess Martin periodinane (2.12g) was added. The reaction mixture was stirred for 1 hour then washed with 2M sodium hydroxide (2x20ml) and brine (10ml) and dried. The dichloromethane solution was concentrated to a volume of about 20ml and used directly in the next stage.

Example 4

This Example illustrates the preparation of (R)-N-(3-phenyl-3-[3,5-difluorophenyl]propyl)-4-[2-(4-methanesulphonylphenylsulphonyl)ethyl]piperidine. (Compound No. 7, Table V).



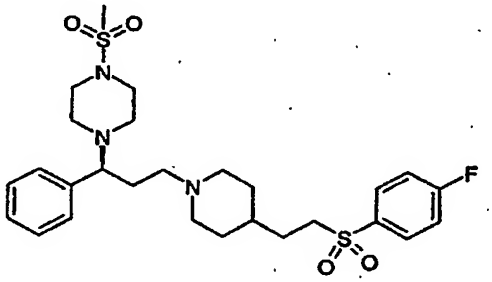
(*R*)-3-(3,5-Difluorophenyl)-3-(4-methanesulfonylphenyl)propionaldehdye (0.357 g, 1.1 mmol; Method E) was dissolved in dichloromethane (3 ml) at room temperature and 4-[2-(4-methanesulphonylphenyl-sulphonyl)ethyl]piperidine hydrochloride (0.368 g, 1 mmol; Method B) was added as a single portion. After stirring for 0.5 h, sodium triacetoxyborohydride (0.211 g, 1 mmol) was added as a single portion and the reaction stirred for a further 1h. The mixture was then washed with saturated aqueous sodium hydrogen carbonate, the organics were separated and poured directly onto an SCX column. Eluting with methanol followed by 20% 7 M ammonia in methanol gave the product (0.319 g, 50%) as a white solid.

NMR: (d6-DMSO): 1.05 (m, 2H), 1.15 (m, 1H), 1.6 (m, 4H), 1.8 (br t, 2H), 2.2 (m, 2H), 2.3 (m, 2H), 2.8 (br d, 2H), 3.4 (m, 6H), 3.5 (m, 2H), 4.3 (br t, 1H), 7.1 (br t, 1H), 7.2 (d, 2H), 7.7 (d, 2H), 7.9 (d, 2H), 8.3 (m, 4H).

LCMS: 640.2 (MH^+).

Example 5

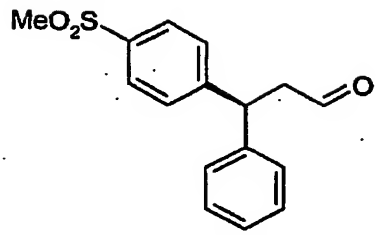
This Example illustrates the preparation of (R or S) N-(3-[4-methanesulphonylpiperazinyl]-3-phenylpropyl)-4-[2-(4-fluorophenylsulphonyl)ethyl]-piperidine [Compound 14, Table III]



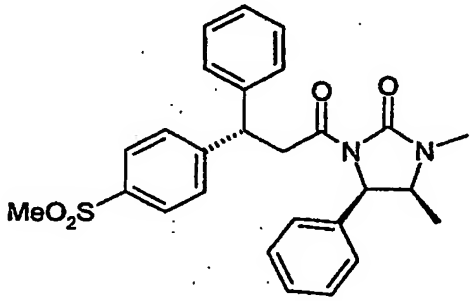
A solution of (R or S) N-(3-chloro-3-phenylpropyl)-4-[2-(4-fluorophenylsulphonyl)-ethyl]-piperidine (Method F; 310 mg) in dichloromethane (6 ml) was added to N-methanesulphonyl-piperazine hydrochloride (150 mg) followed by triethylamine (313 µl). The mixture was stirred for 48 hours, diluted with dichloromethane (5 ml) and MP-carbonate resin (1.34g), PS-isocyanate resin (682 mg) and PS-thiophenol resin (577 mg) were added. The mixture was stirred for 5 hours, filtered and the resins were washed with 10% methanol in dichloromethane (2 X 25 ml). The combined filtrates were evaporated to dryness and the residue was passed through a 20g Isolute column eluted with a solvent gradient of ethyl acetate-10% methanol/ethyl acetate to give the title compound, yield 81 mg. NMR: ($CDCl_3$): 1.12-1.32 (m, 4H), 1.52-1.66 (m, 4H), 1.76-1.93 (m, 3H), 2.08 (m, 1H), 2.21 (m, 1H), 2.47-2.51 (m, 4H), 2.71 (s, 3H), 2.77-2.88 (m, 2H), 3.03-3.10 (m, 2H), 3.12-3.21 (m, 4H), 3.37 (m, 1H), 7.14 (d, 2H), 7.15-7.32 (m, 5H), 7.88 (m, 2H); MS 552 (MH^+).

Method A

(*S*)-3-Phenyl-3-(4-methanesulfonylphenyl)propionaldehyde



Step 1: Preparation of (4*R*, 5*S*)-1-[(*S*)-3-(4-methanesulfonyl-phenyl)-3-phenyl-propionyl]-3,4-dimethyl-5-phenyl-imidazolidin-2-one



To a mixture of copper (I) iodide (960mg, 5.0mmol) and THF (20mL) was added *N,N,N',N'*-tetramethylethylenediamine (0.83mL, 5.5mmol) and the resulting mixture was stirred at room temperature for 10min. then cooled to –78°C. Phenylmagnesium bromide (5.0mL, 1M in THF, 5.0mmol) was added and the resulting mixture stirred at –78°C for 15min. A solution of di-n-butylboron triflate (3.0mL, 1M in diethyl ether, 3.0mmol) and (*E*)-(4*R*, 5*S*)-1-(3-[4-methanesulfonylphenyl]acryloyl)-3,4-dimethyl-5-phenyl-imidazolidin-2-one (step 4 below), 1.0g, 2.51mmol) in THF (15mL) was added and the resulting mixture was stirred whilst allowing to warm to room temperature for 18h. The reaction mixture was washed with saturated aqueous ammonium chloride, water and brine, dried ($MgSO_4$) and evaporated. The residue was purified by eluting through a 20g Bond Elut with gradient of isohexane to ethyl acetate giving the sub-titled compound (1.49g, 100%); NMR ($CDCl_3$): 0.78 (d, 3H), 2.82 (s, 3H), 3.00 (s, 3H), 3.78 (dd, 1H), 3.80 (m, 1H), 3.98 (dd, 1H), 4.72 (m, 1H), 5.19 (d, 1H), 6.99 (m, 2H), 7.22 (m, 8H), 7.48 (d, 2H), 7.79 (d, 2H); MS: 477 (MH+).

Step 2: Preparation of (*S*)-3-phenyl-3-(4-methanesulphonylphenyl)propan-1-ol

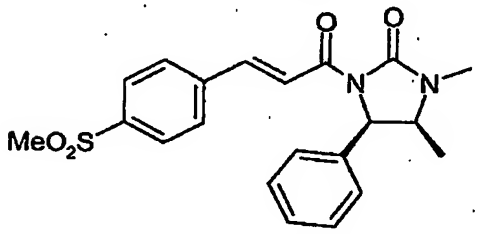
To a solution of (4*R*, 5*S*)-1-[(*S*)-3-(4-methanesulphonyl-phenyl)-3-phenyl-propionyl]-3,4-dimethyl-5-phenyl-imidazolidin-2-one (846mg, 1.78mmol) in THF (20mL) at 0°C was added lithium aluminium hydride (3.6mL, 1M in THF, 3.6mmol) and the resulting mixture was stirred for 15min. The reaction was quenched by the addition of 2M aqueous sodium

hydroxide. The phases were separated and the organic phase pre-absorbed onto a Bond Elut and eluted with a gradient of isohexane to ethyl acetate giving the sub-titled compound as a white solid (285mg, 55%); NMR ($CDCl_3$): 1.63 (br s, 1H), 2.33 (m, 2H), 3.00 (s, 3H), 3.59 (t, 2H), 4.28 (t, 1H), 7.23 (m, 5H), 7.43 (d, 2H), 7.82 (d, 2H).

Step 3: Preparation of the title compound

To a solution of (*S*)-3-phenyl-3-(4-methanesulfonylphenyl)propan-1-ol (244mg, 0.84mmol) in DCM (5mL) was added Dess-Martin periodinane (392mg, 0.92mmol) and the resulting mixture was stirred at room temperature for 1.5h. The mixture was washed with 2M aqueous sodium hydroxide (2 x 10mL), dried and evaporated to give the title compound.

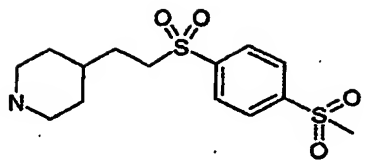
Step 4: Preparation of *E*-(4*R*, 5*S*)-1-(3-[4-Methanesulphonylphenyl]acryloyl)-3,4-dimethyl-5-phenyl-imidazolidin-2-one



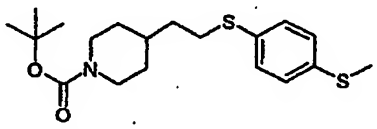
To a stirred solution of 3-(4-methanesulphonylphenyl)acrylic acid (7.14g, 31.5mmol) in DCM (10mL) was added thionyl chloride (3mL, 34.7mmol) dropwise and the resulting mixture was stirred at room temperature for 18h. To this solution was added DIPEA (5.04mL, 28.9mmol) dropwise at room temperature. The resulting solution was added to a stirred solution of (4*R*, 5*S*)-3,4-dimethyl-5-phenyl-imidazolidin-2-one (5.0g, 26.3mmol) in DCM (20mL) and DIPEA (4.58mL, 26.9mmol) and the resulting mixture stirred at room temperature for 4h. The mixture was washed with water and brine, pre-absorbed onto a Bond Elut and eluted with a gradient of isohexane to ethyl acetate giving the title compound as a solid (7.61g, 73%); NMR ($CDCl_3$): 0.84 (d, 3H), 2.89 (s, 3H), 3.04 (s, 3H), 3.98 (m, 1H), 5.42 (d, 1H), 7.20 (m, 2H), 7.32 (m, 3H), 7.69 (d, 1H), 7.74 (d, 2H), 7.93 (d, 2H), 8.31 (d, 1H); MS: 399 (MH+).

Method B

4-[2-(4-Methanesulphonylphenylsulphonyl)ethyl]piperidine

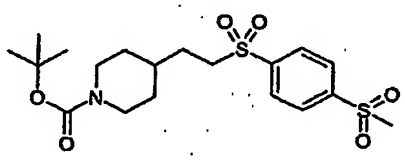


Step 1 Preparation of N-tert-butoxycarbonyl-4-[2-(4-methylthiophenylthio)ethyl]piperidine



4-Methylthiobenzenethiol (1.16g) was added to a suspension of sodium hydride (297mg of 60% dispersion in mineral oil) in DMF (20ml) at 0°C and stirred at this temperature for 30 minutes. N-tert-butoxycarbonyl-4-[2-(4-toluenesulphonyloxy)ethyl]-piperidine (CAS No. 89151-45-1) (2.84g) was added, the reaction mixture was allowed to warm to room temperature and was stirred for 16 hours. The reaction mixture was evaporated to dryness and the residue obtained was dissolved in dichloromethane (30 ml) and the solution was washed with water (20 ml) and brine (20 ml) and dried. The residue obtained on removal of the solvent was chromatographed on a 50g silica Bond Elut column eluting with a solvent gradient of isohexane-50% ethyl acetate/isohexane. Yield 2.5g, MH^+ 268.

Step 2 Preparation of N-tert-butoxycarbonyl-4-[2-(4-methylsulphonylphenylsulphonyl)ethyl]-piperidine.



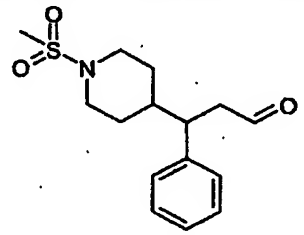
m-Chloroperbenzoic acid (5.64g) was added to a solution of N-tert-butoxycarbonyl-4-[2-(4-methylthiophenylthio)ethyl]piperidine (2.1g) in dichloromethane (90 ml) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 16 hours. The reaction mixture was washed with saturated aqueous sodium bicarbonate solution (20 ml), water (20 ml) and brine (20 ml) then dried and evaporated to dryness. The product was chromatographed on a 50g silica Bond Elut column eluting with a solvent gradient of 20% ethyl acetate/isohexane-ethyl acetate to give the product, yield 1.82g, MH^+ 375.9.

Step 3 Preparation of title compound

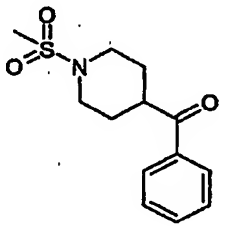
Trifluoroacetic anhydride (5 ml) was added to a solution of N-tert-butoxycarbonyl-4-[2-(4-methylsulphonylphenylsulphonyl)ethyl]piperidine (1.94g) in dichloromethane (20 ml) and was allowed to stand at room temperature for 1 hour. The reaction mixture was evaporated to dryness and the residue was dissolved in 2M sodium hydroxide (15 ml) and extracted with dichloromethane (3x20 ml). The combined dichloromethane extracts were dried and evaporated to dryness to give the title compound, yield 1.3g, MH^+331.9.

Method C

3-Phenyl-3-(N-methanesulphonylpiperidin-4-yl)propionaldehyde

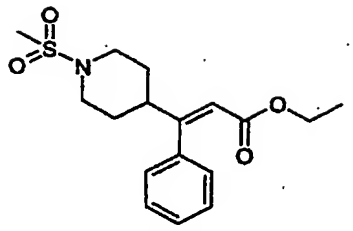


Step 1 Preparation of 4-benzoyl-1-methanesulphonylpiperidine



Methanesulphonyl chloride was added to a stirred slurry of 4-benzoylpiperidine hydrochloride (4.51g) and triethylamine (8.35ml) in dichloromethane (100ml) at 0°C. The reaction mixture was allowed to warm to room temperature and was stirred for 16 hours. The mixture was diluted with dichloromethane (50ml) and washed with ammonium chloride solution (2x25ml) and brine (25ml), dried and evaporated to dryness to give 4-benzoyl-1-methanesulphonylpiperidine as a white solid, yield 3.98g. NMR ($CDCl_3$): 1.93 (m, 4H), 2.81 (s, 3H), 2.98 (d-t, 2H), 3.40 (m, 1H), 3.77 (m, 2H), 7.43 (t, 2H), 7.57 (t, 1H), 7.89 (d, 2H).

Step 2 Preparation of ethyl 3-phenyl-3-(N-methanesulphonylpiperidin-4-yl)acrylate.

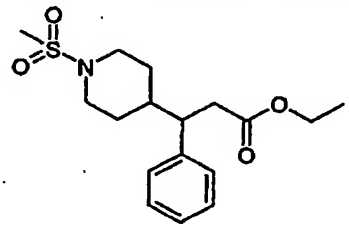


Lithium bis(trimethylsilyl)amide (16.3ml of a 1M solution in THF) was added dropwise to a solution of triethylphosphonoacetate (2.93ml) in THF at 0°C under an argon atmosphere and the mixture was stirred for 30 minutes. A slurry of 4-benzoyl-1-methanesulphonylpiperidine (3.96g) in THF (30ml) was added, the reaction mixture was allowed to warm to room temperature and stirring was continued for 24 hours. The reaction mixture was diluted with dichloromethane (80ml) and water (80ml). The organic layer was washed with water and the combined aqueous extracts were in turn extracted with dichloromethane (50ml). The combined dichloromethane extracts were washed with brine (25ml), dried and evaporated to dryness. The residue was chromatographed on a 90g Biotage column eluted with a solvent gradient (30-5-% ethyl acetate/isohexane to give a less polar fraction (1.62g) and a more polar fraction (0.53g). Both fractions (cis/trans isomers) were combined and used for the next step.

Less polar NMR ($CDCl_3$): 1.27 (t, 3H), 1.69 (m, 2H), 1.81 (d, 2H), 2.72 (s, 3H), 2.72 (t, 2H), 3.81 (d, 2H), 3.88 (m, 1H), 4.21 (q, 2H), 5.78 (s, 1H), 7.11 (m, 2H), 7.27 (m, 3H).

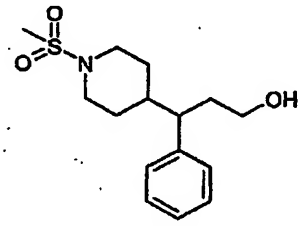
More polar NMR ($CDCl_3$): 1.01 (t, 3H), 1.56 (m, 2H), 1.85 (d, 2H), 2.31 (m, 1H), 2.63 (t, 2H), 2.74 (s, 3H), 3.83 (d, 2H), 3.92 (q, 3H), 5.82 (s, 1H), 7.04 (d, 2H), 7.30 (m, 3H).

Step 3 Preparation of ethyl 3-phenyl-3-(N-methanesulphonylpiperidin-4-yl)propionate



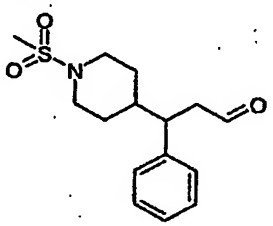
A solution of ethyl 3-phenyl-3-(N-methanesulphonylpiperidin-4-yl)acrylate (2.06g) in ethanol (30ml) was hydrogenated over 24 hours under a hydrogen filled balloon using 20% palladium hydroxide as catalyst. The reaction mixture was filtered through Celite and the filtrate evaporated to dryness. The product obtained was used for the next step without further purification. MH^+340.

Step 4 3-Phenyl-3-(N-methanesulphonylpiperidin-4-yl)propan-1-ol.



A solution of ethyl 3-phenyl-3-(N-methanesulphonylpiperidin-4-yl)propionate (2g) in THF (10ml) was added to a suspension of lithium aluminium hydride (232mg) in THF (20ml) at 0°C under argon over 30 minutes. The reaction mixture was allowed to warm to room temperature and stirred for 2 hours. Water (10ml) was added followed by magnesium sulphate (10g). The reaction mixture was filtered and the filtrate evaporated to dryness to give the product as a white foam, yield 1.57g. NMR ($CDCl_3$): 1.40 (m, 4H), 1.57 (m, 1H), 1.78 (m, 1H), 2.01 (m, 2H), 2.45 (m, 2H), 2.58 (t, 1H), 2.70 (m, 3H), 3.31 (m, 1H), 3.42 (m, 1H), 3.67 (d, 1H), 3.80 (d, 1H), 7.04 (d, 1H), 7.19 (t, 1H), 7.29 (q, 2H).

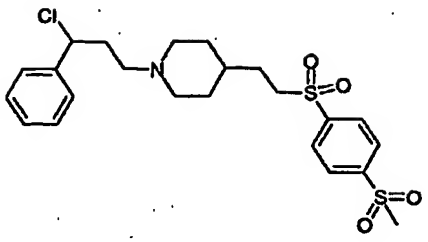
Step 5 Preparation of the title compound



Dess-Martin periodinane (739mg) was added to a stirred solution of 3-phenyl-3-(N-methanesulphonylpiperidin-4-yl)propan-1-ol (454mg) in dichloromethane (8ml) and stirring was continued for 2 hours. The reaction mixture was diluted with dichloromethane (100ml) and washed with 2M sodium hydroxide (2x50ml), brine (50ml) and dried. The product obtained on removal of the solvent was used in subsequent steps without purification.

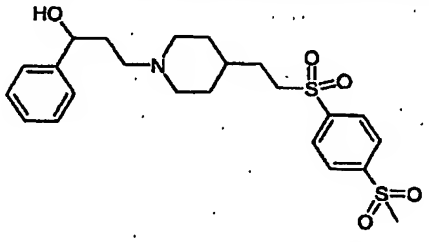
Method D

N-(3-chloro-3-phenylpropyl)-4-[2-(4-methanesulphonylphenylsulphonyl)ethyl]-piperidine



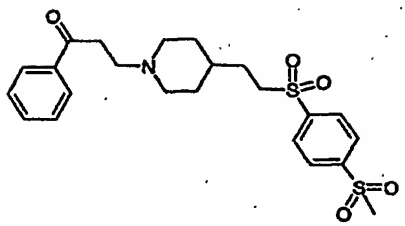
Triethylamine (0.73 ml) was added to a solution of N-(3-hydroxy-3-phenylpropyl)-4-[2-(4-methanesulphonylphenylsulphonyl)ethyl]-piperidine (1.22g) in dichloromethane (20 ml) followed by methanesulphonyl chloride (0.0.33 g) and the mixture was stirred for 18 hours at room temperature. The reaction mixture was washed successively with water (25 ml) and brine (25 ml) and dried. The residue obtained after removal of the solvent was chromatographed on a 20g silica Bond Elut column eluted with a solvent gradient of ethyl acetate-20% methanol/ethyl acetate to give the title compound, yield 0.73g, MH^+ 483.99. NMR($CDCl_3$) : 1.3 (m, 3H) 1.6 (m, 4H) 1.9 (m, 2H) 2.1-2.3 (m, 2H) 2.4 (m, 2H) 2.8-2.9 (m, 2H) 3.1 (s, 3H) 3.2 (m, 2H) 5.0 (m, 1H) 7.3 (m, 5H) 8.2 (m, 4H).

N-(3-hydroxy-3-phenylpropyl)-4-[2-(4-methanesulphonylphenylsulphonyl)ethyl]-piperidine



Sodium borohydride (100mg) was added in portions to a solution of N-(3-oxo-3-phenylpropyl)-4-[2-(4-methanesulphonylphenylsulphonyl)ethyl]-piperidine (1.22g) in ethanol (20ml) at room temperature and was stirred for 18 hours. The reaction mixture was evaporated to dryness and the residue was dissolved in dichloromethane (30ml) and this solution was washed with water (25ml), brine (25ml) and dried. Removal of the solvent gave the title compound as white solid, yield 1.21g, MH^+ 465.98.

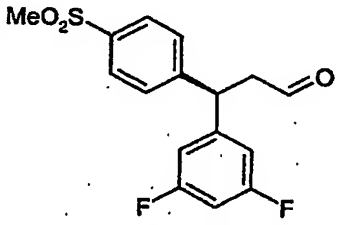
N-(3-oxo-3-phenylpropyl)-4-[2-(4-methanesulphonylphenylsulphonyl)ethyl]-piperidine



3-Chloropropiophenone (0.726g) was added to a mixture of 4-[2-(4-methanesulphonylphenylsulphonyl)ethyl]-piperidine (1.3g) (prepared as described in method B) and potassium carbonate (1.09g) in DMF (20ml) and the mixture was stirred at room temperature for 1 hour. The reaction mixture was evaporated to dryness and the residue was dissolved in dichloromethane (30ml). The dichloromethane solution was washed with water (25ml), brine (25ml) and dried. The residue obtained after removal of the solvent was chromatographed on a 50g silica Bond Elut column eluted with a solvent gradient of ethyl acetate-20% methanol/ethyl acetate to give the title compound as a white solid, yield 1.22g, MH^+ 463.97. NMR($CDCl_3$) : 1.2-1.4 (m, 3H) 1.6 (m, 4H) 2.0 (m, 2H) 2.8 (m, 2H) 2.9 (m, 2H) 3.1-3.2 (m 7H) 7.4 (m, 2H) 7.5(m, 1H) 7.9 (M, 2H) 8.2 (m, 4H).

Method E

(*R*)-3-(3,5-Difluorophenyl)-3-(4-methanesulfonylphenyl)propionaldehdye

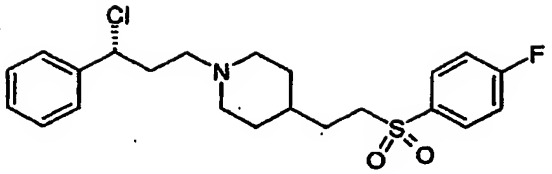


This was prepared from (4*R*, 5*S*)-1-(3-[4-methanesulfonylphenyl]acryloyl)-3,4-dimethyl-5-phenyl-imidazolidin-2-one and 3,5-difluorophenylmagnesium bromide using a method similar to that used to prepare (*S*)-3-phenyl-3-(4-methanesulfonyl-phenyl)propionaldehyde from phenylmagnesium bromide (Method A); NMR ($CDCl_3$): 3.05 (s, 3H), 3.20 (d, 2H), 4.72 (t, 1H), 6.75 (m, 3H), 7.35 (d, 2H), 7.88 (d, 2H), 9.75 (s, 1H).

Method F

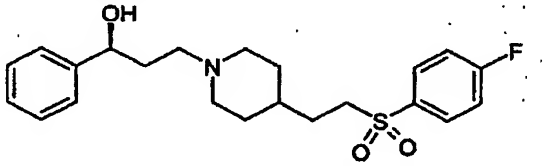
(S) N-(3-hydroxy-3-phenylpropyl)-4-[2-(4-fluorophenylsulphonyl)ethyl]-piperidine

Step 1: (R or S) N-(3-chloro-3-phenylpropyl)-4-[2-(4-fluorophenylsulphonyl)ethyl]-piperidine



Methanesulphonyl chloride (158 µl) was added to a solution of (S) N-(3-hydroxy-3-phenylpropyl)-4-[2-(4-fluorophenylsulphonyl)ethyl]-piperidine (600 mg) and triethylamine (417 µl) in dichloromethane (10 ml) maintained at 0 °C under an argon atmosphere. The reaction mixture was allowed to warm to room temperature and was stirred for 18 hours. The reaction mixture was diluted with dichloromethane (50 ml) and washed with saturated amonium chloride solution (2 X 25 ml) and brine (25 ml) and dried. Removal of the solvent gave the title compound which was used without further purification. NMR: ($CDCl_3$): 1.18-2.24 (m, 13H), 2.78 (m, 1H), 2.84 (m, 1H), 3.04 (1H, m), 4.92 (t, 1H), 7.20-7.40 (m, 7H), 7.91 (m, 2H); MS 424 (MH^+).

Step 2: (S) N-(3-hydroxy-3-phenylpropyl)-4-[2-(4-fluorophenylsulphonyl)ethyl]-piperidine



A solution of (S)-1-phenyl-3-(4-toluenesulphonyl)oxypropan-1-ol (459 mg) in dioxane (10ml) was added to a suspension of 4-[2-(4-fluorophenylsulphonyl)ethyl]piperidine (407 mg) and potassium carbonate (414 mg) and the mixture was heated at 95 °C for 17 hours. The reaction mixture was allowed to cool and was partitioned between dichloromethane (100 ml) and water (50 ml). The organic layer was collected and washed with water (50 ml), brine (50 ml) and dried. Removal of the solvent gave the title compound, yield 607 mg. NMR: ($CDCl_3$): 1.18-1.69 (m, 8H), 1.82 (m, 3H), 2.02 (m, 1H), 2.48 (m, 1H), 2.62 (m, 1H), 2.93 (d, 1H), 3.05 (m, 3H), 4.89 (m, 1H), 7.21-7.40 (m, 7H), 7.92 (m, 2H); MS 406 (MH^+).

Example 6

The ability of compounds to inhibit the binding of RANTES was assessed by an *in vitro* radioligand binding assay. Membranes were prepared from Chinese hamster ovary cells which expressed the recombinant human CCR5 receptor. These membranes were incubated with 0.1nM iodinated RANTES, scintillation proximity beads and various concentrations of

the compounds of the invention in 96-well plates. The amount of iodinated RANTES bound to the receptor was determined by scintillation counting. Competition curves were obtained for compounds and the concentration of compound which displaced 50% of bound iodinated RANTES was calculated (IC_{50}). Preferred compounds of formula (I) have an IC_{50} of less than 50μM.

Example 7

The ability of compounds to inhibit the binding of MIP-1α was assessed by an *in vitro* radioligand binding assay. Membranes were prepared from Chinese hamster ovary cells which expressed the recombinant human CCR5 receptor. These membranes were incubated with 0.1nM iodinated MIP-1α , scintillation proximity beads and various concentrations of the compounds of the invention in 96-well plates. The amount of iodinated MIP-1α bound to the receptor was determined by scintillation counting. Competition curves were obtained for compounds and the concentration of compound which displaced 50% of bound iodinated MIP-1α was calculated (IC_{50}). Preferred compounds of formula (I) have an IC_{50} of less than 50μM.

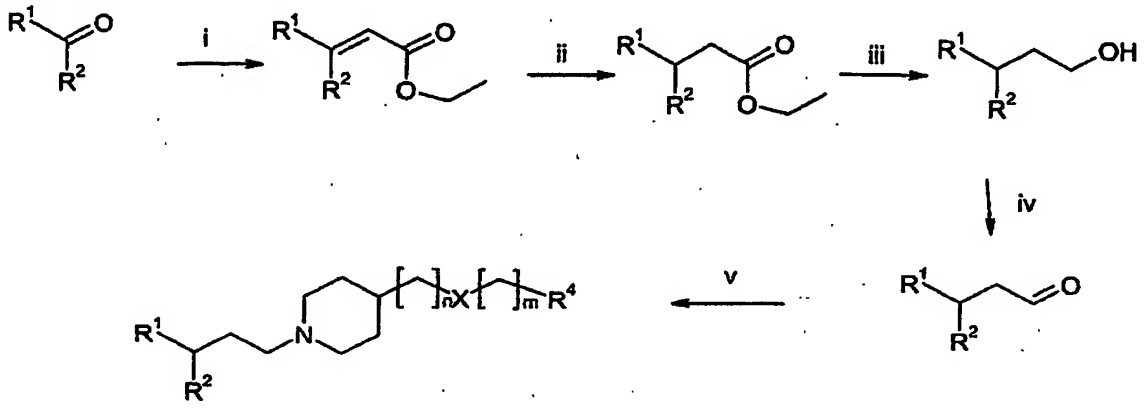
Results from this test for certain compounds of the invention are presented in Table IV. In Table IV the results are presented as Pic50 values. A Pic50 value is the negative log (to base 10) of the IC_{50} result, so an IC50 of 1μM (that is 1×10^{-6}M) gives a Pic50 of 6. If a compound was tested more than once then the data below is an average of the probative tests results.

TABLE IV

Table Number	Compound number	Pic50
1	6	6.91
1	8	8.58
1	13	7.9
1	16	8.63
4	2	8.8
7	2	8.95

Scheme 1

To prepare compounds of the invention, for example wherein R^1 is aryl or C-linked piperidine.

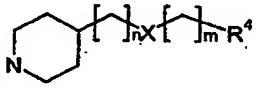


i Wittig reaction (eg LHDMS, triethylphosphonoacetate)

ii Catalytic hydrogenation (eg H_2, 10% Pd/C)

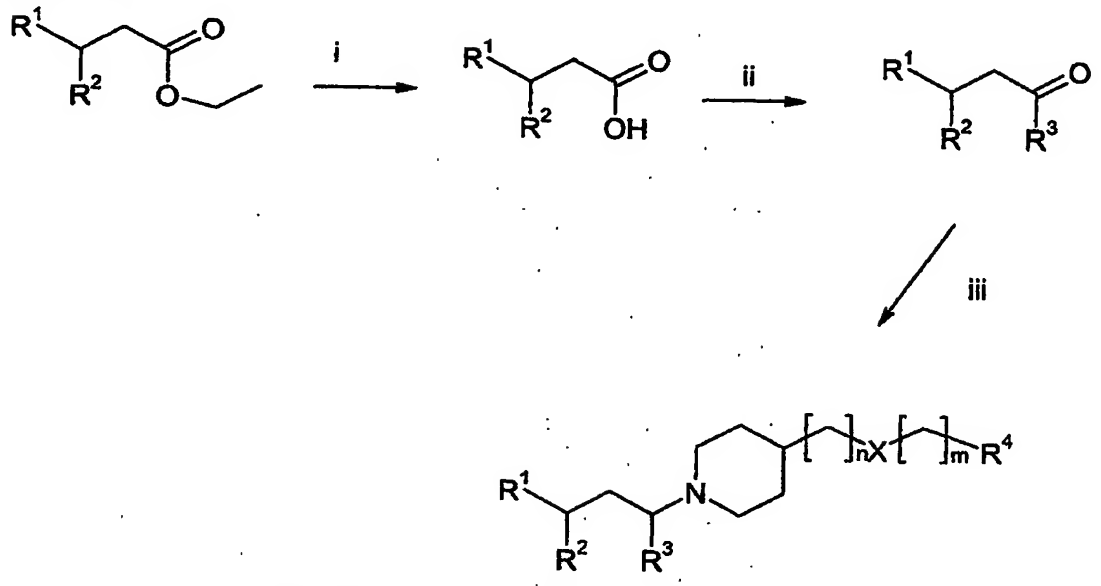
iii Reduction (eg LAH)

iv Oxidation (eg Dess-Martin oxidation)

v reductive ammination with  (eg using sodium triacetoxyborohydride)

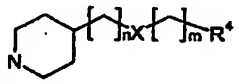
Scheme 2

To prepare compounds of the invention, for example wherein R^1 is aryl or C-linked piperidine.



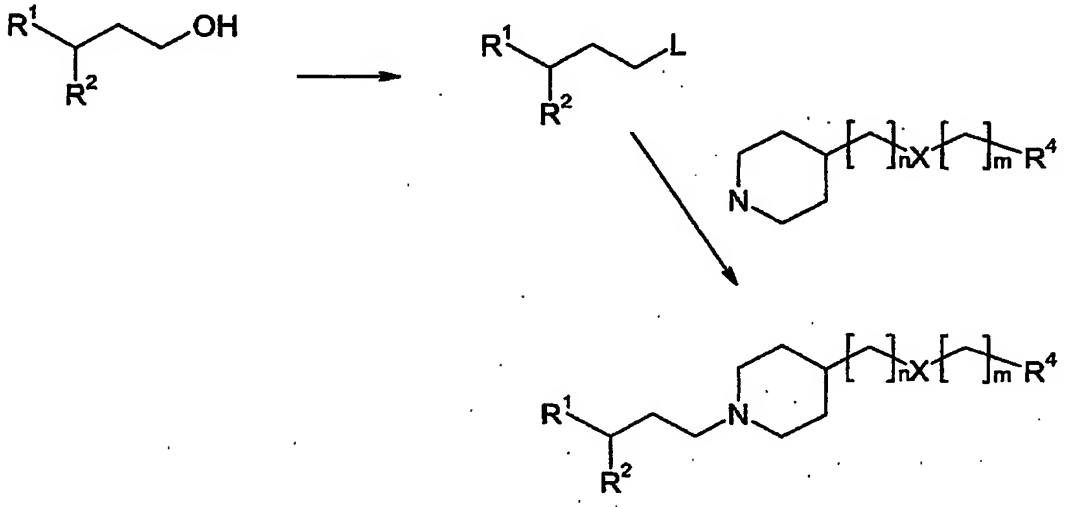
i Base hydrolysis (eg LiOH, MeOH/H_2O)

ii MeMgCl, R^3MgBr, Et_2O

iii reductive amination  in presence of titanium tetra-isopropoxide (eg using sodium triacetoxyborohydride)

Scheme 3

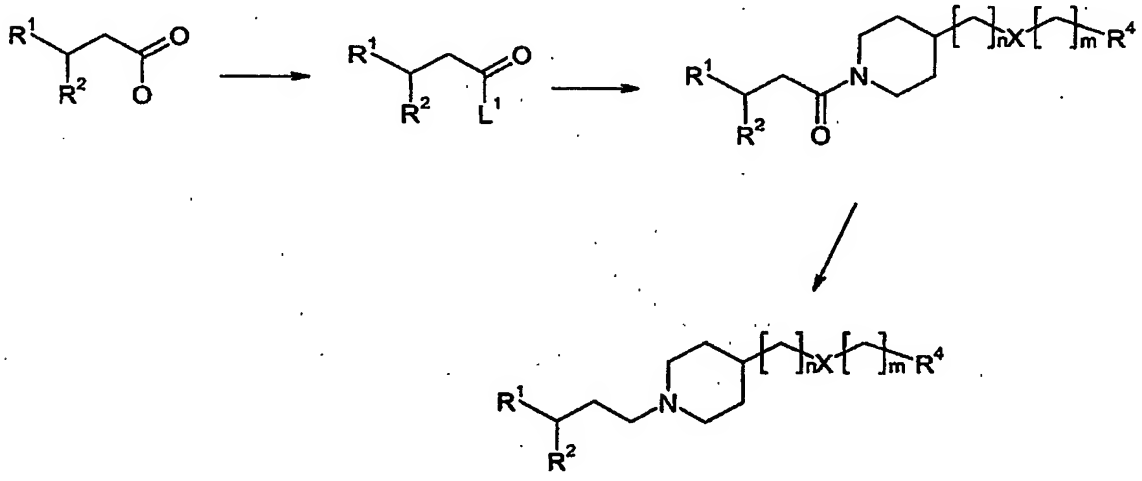
To prepare compounds of the invention, for example wherein R^1 is aryl, heteroaryl, heterocyclyl or $NR^{13}C(O)R^{14}$.



in which L is an activated group, such as halogen, mesylate, tosylate or triflate.

Scheme 4

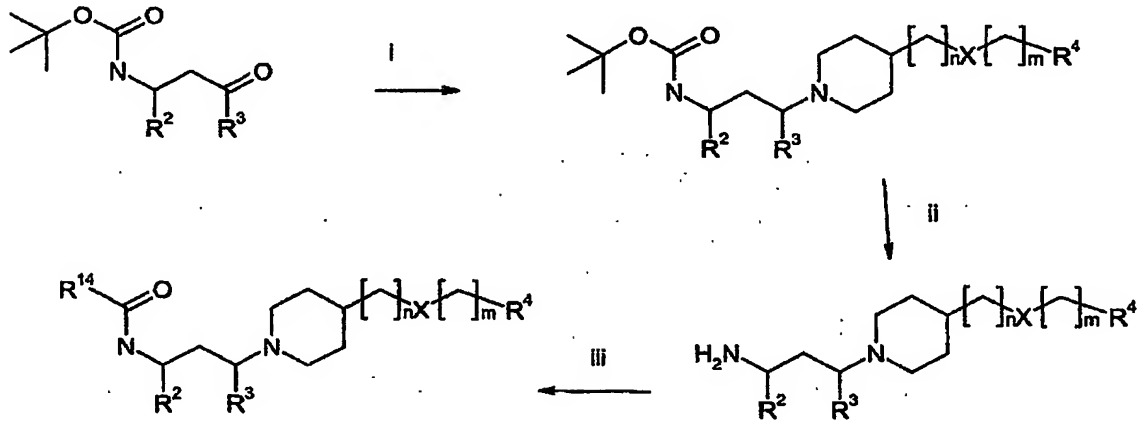
To prepare compounds of the invention, for example wherein R^1 is aryl, heteroaryl, heterocyclyl or $NR^{13}C(O)R^{14}$.



in which L^1 is a halogen, an activated ester or a complex formed with a carbodiimide.

Scheme 5

To prepare compounds of the invention, for example wherein R^1 is $NR^{13}C(O)R^{14}$.



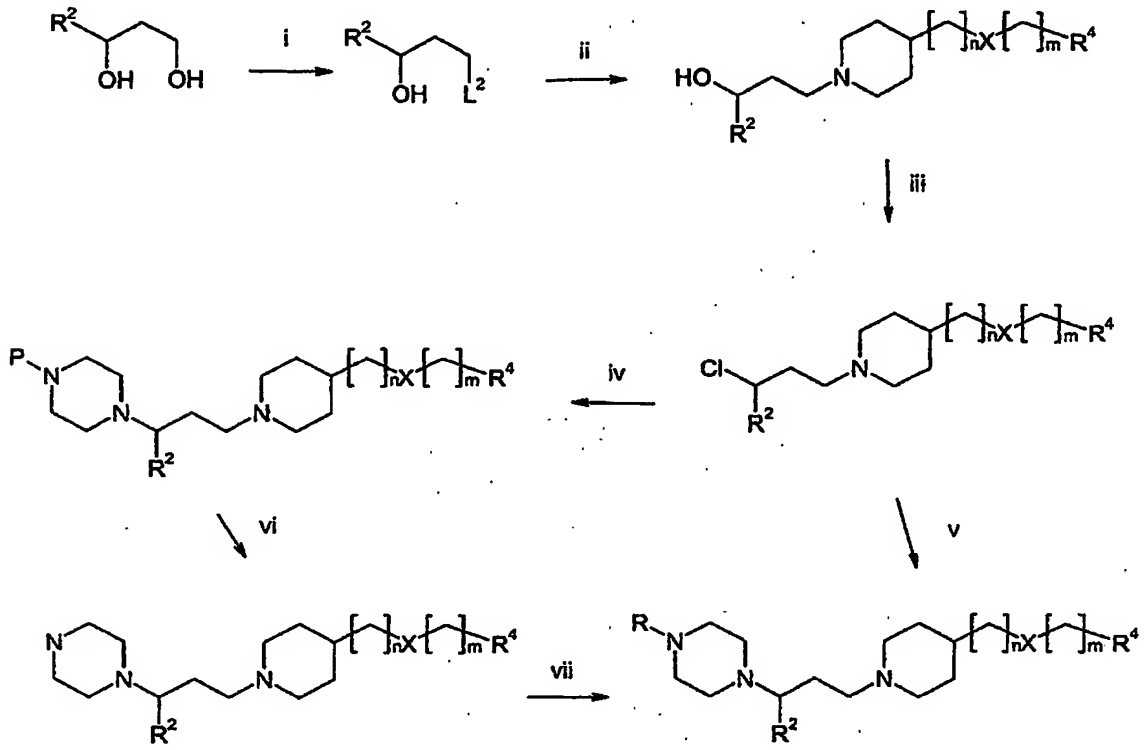
i reductive amination (if R^3 is H can use sodium triacetoxyborohydride; if R^3 is alkyl can use titanium tetra-isopropoxide and sodium triacetoxyborohydride)

ii Deprotection (eg TFA)

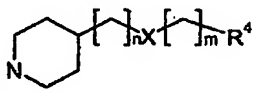
iii amide bond formation (eg acid chloride, active ester or carbodiimide mediated)

Scheme 5

To prepare compounds of the invention, for example wherein R^1 is piperazine.



i Conversion of an OH to a leaving group (eg tosyl chloride (L^2 is Tosylate) or mesyl chloride (L^2 is Mesylate))

ii displacement reaction with  (eg in presence of triethylamine)

iii Mesyl chloride, DCM 0°C

iv Displacement reaction with mono-protected piperazine (P is a protecting group)

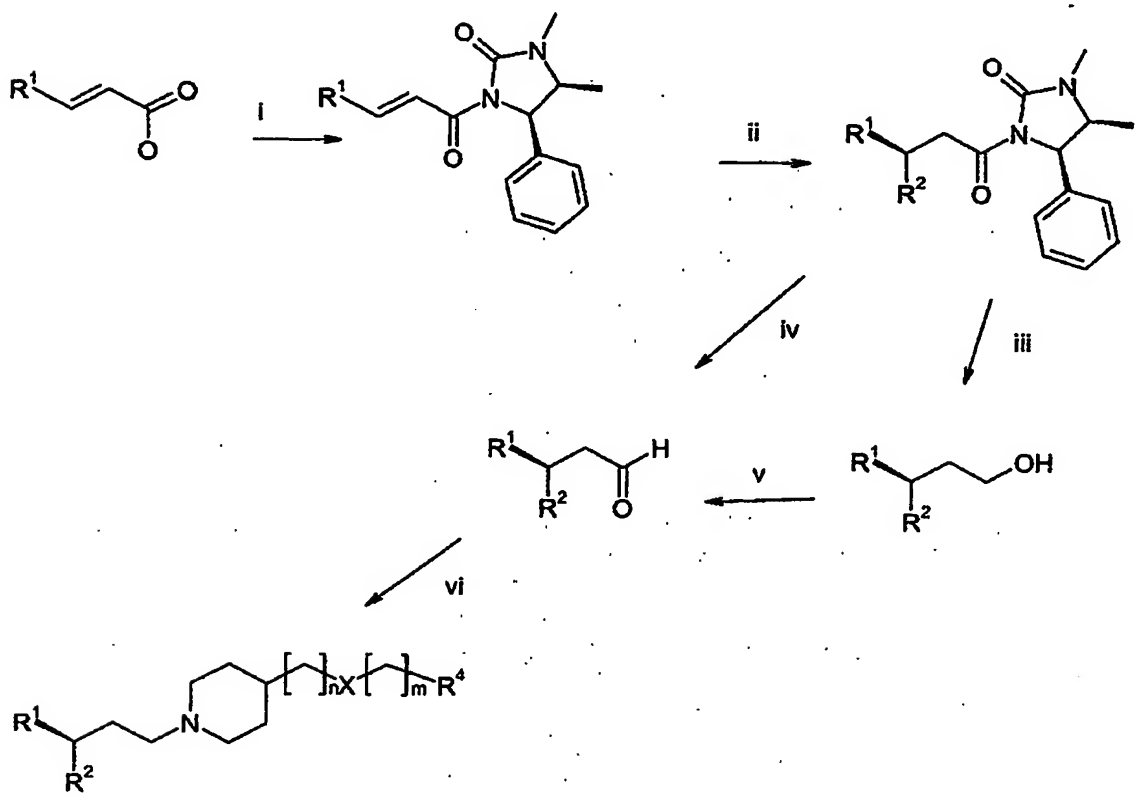
v Displacement reaction with R substituted piperazine

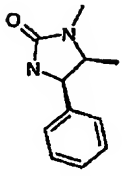
vi Deprotection (TFA for Boc, hydrogenation for Cbz)

vii Depending on R, acylation, sulphonylation, alkylation, reductive amination

Scheme 6

To prepare compounds of the invention, for example wherein R^1 is aryl or piperidine.

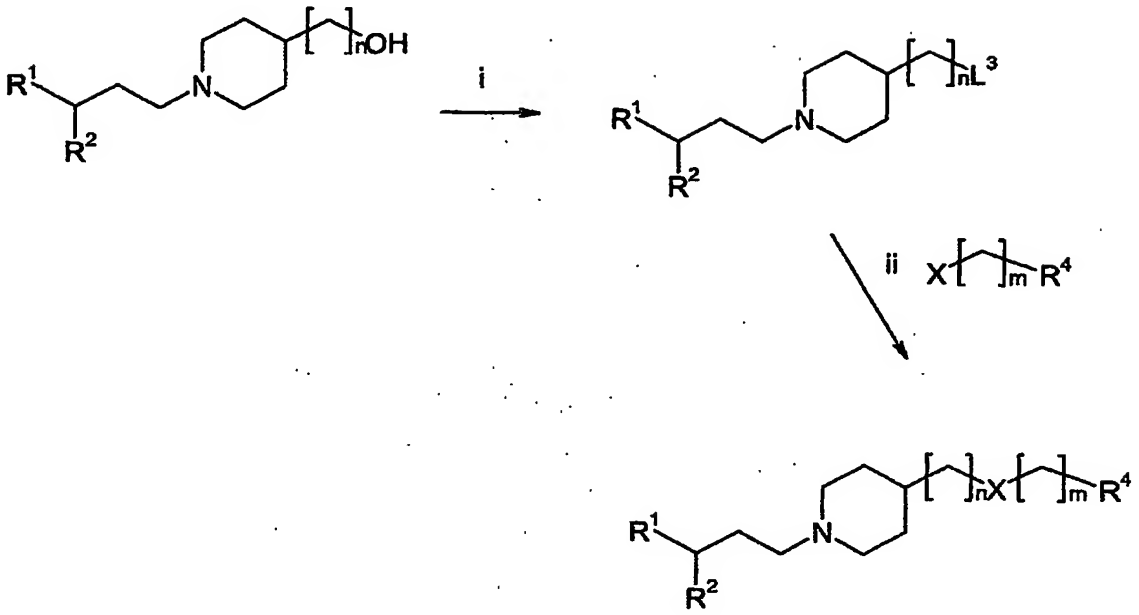




i	activation of acid group and coupling with chiral auxiliary (eg $SOCl_2$,	)
ii	1,4-addition of organocuprate (eg R^2MgBr, Cu(I)I, TMEDA, di-butylboron triflate)	
iii	reduction (eg lithium aluminium hydride)	
iv	Dibal	
v	Oxidation (eg Dess-Martin reagent)	
vi	reductive amination (eg with sodium triacetoxyborohydride)	

Scheme 7

To prepare compounds of the invention.

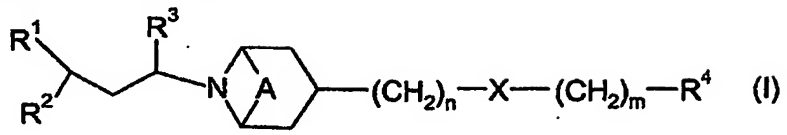


i activation via halide, tosylate, mesylate, triflate

ii base catalysed displacement

CLAIMS

1. A compound of formula (I):



wherein:

A is absent or is $(CH_2)_2$;

R^1 is C_{1-8} alkyl, $C(O)NR^{10}R^{11}$, $C(O)_2R^{12}$, $NR^{13}C(O)R^{14}$, $NR^{15}C(O)NR^{16}R^{17}$, $NR^{18}C(O)_2R^{19}$, heterocyclyl (for example piperidine, piperazine, pyrrolidine or azetidine), aryl or heteroaryl;

R^{10}, R^{13}, R^{15}, R^{16} and R^{18} are hydrogen or C_{1-6} alkyl;

R^{11}, R^{12}, R^{14}, R^{17} and R^{19} are C_{1-8} alkyl (optionally substituted by halo, hydroxy, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl (optionally substituted by halo), C_{5-6} cycloalkenyl, $S(C_{1-4}$ alkyl), $S(O)(C_{1-4}$ alkyl), $S(O)_2(C_{1-4}$ alkyl), heteroaryl, aryl, heteroaryloxy or aryloxy), aryl, heteroaryl, C_{3-7} cycloalkyl (optionally substituted by halo or C_{1-4} alkyl), C_{4-7} cycloalkyl fused to a phenyl ring, C_{5-7} cycloalkenyl, or, heterocyclyl (itself optionally substituted by oxo, $C(O)(C_{1-6}$ alkyl), $S(O)_k(C_{1-6}$ alkyl), halo or C_{1-4} alkyl); or R^{11}, R^{12}, R^{14} and R^{17} can also be hydrogen;

or R^{10} and R^{11}, and/or R^{16} and R^{17} may join to form a 4-, 5- or 6-membered ring which optionally includes a nitrogen, oxygen or sulphur atom, said ring being optionally substituted by C_{1-6} alkyl, $S(O)_l(C_{1-6}$ alkyl) or $C(O)(C_{1-6}$ alkyl);

R^2 C_{1-6} alkyl, phenyl, heteroaryl or C_{3-7} cycloalkyl;

R^3 H or C_{1-4} alkyl;

R^4 is aryl or heteroaryl;

X is O or $S(O)_p$;

m and n are, independently, 0, 1, 2 or 3, provided m + n is 1 or more, and provided that when X is O then m and n are not both 1;

unless specified otherwise aryl, phenyl and heteroaryl moieties are independently optionally substituted by one or more of halo, cyano, nitro, hydroxy, $OC(O)NR^{20}R^{21}$, $NR^{22}R^{23}$, $NR^{24}C(O)R^{25}$, $NR^{26}C(O)NR^{27}R^{28}$, $S(O)_2NR^{29}R^{30}$, $NR^{31}S(O)_2R^{32}$, $C(O)NR^{33}R^{34}$, CO_2R^{36}, $NR^{37}CO_2R^{38}$, $S(O)_qR^{39}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl,

C_{3-10} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy(C_{1-6})alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, phenyl, phenyl(C_{1-4})alkyl, phenoxy, phenylthio, phenylS(O), phenylS(O)$_2$, phenyl(C_{1-4})alkoxy, heteroaryl, heteroaryl(C_{1-4})alkyl, heteroaryloxy or heteroaryl(C_{1-4})alkoxy; wherein any of the immediately foregoing phenyl and heteroaryl moieties are optionally substituted with halo, hydroxy, nitro, S(C_{1-4} alkyl), S(O)(C_{1-4} alkyl), S(O)$_2$(C_{1-4} alkyl), S(O)$_2$NH$_2$, S(O)$_2$NH(C_{1-4} alkyl), S(O)$_2$N(C_{1-4} alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, C(O)NH$_2$, C(O)NH(C_{1-4} alkyl), C(O)N(C_{1-4} alkyl)$_2$, CO$_2$H, CO$_2$(C_{1-4} alkyl), NHC(O)(C_{1-4} alkyl), NHS(O)$_2$(C_{1-4} alkyl), CF_3 or OCF_3;

unless otherwise stated heterocyclyl is optionally substituted by C_{1-6} alkyl [optionally substituted by phenyl {which itself optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, cyano, nitro, CF_3, OCF_3, (C_{1-4} alkyl)C(O)NH, S(O)$_2$NH$_2$, C_{1-4} alkylthio, S(O)(C_{1-4} alkyl) or S(O)$_2$(C_{1-4} alkyl)} or heteroaryl {which itself optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, cyano, nitro, CF_3, (C_{1-4} alkyl)C(O)NH, S(O)$_2$NH$_2$, C_{1-4} alkylthio, S(O)(C_{1-4} alkyl) or S(O)$_2$(C_{1-4} alkyl)}], phenyl {optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, cyano, nitro, CF_3, OCF_3, (C_{1-4} alkyl)C(O)NH, S(O)$_2$NH$_2$, C_{1-4} alkylthio, S(O)(C_{1-4} alkyl) or S(O)$_2$(C_{1-4} alkyl)}, heteroaryl {optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, cyano, nitro, CF_3, (C_{1-4} alkyl)C(O)NH, S(O)$_2$NH$_2$, C_{1-4} alkylthio, S(O)(C_{1-4} alkyl) or S(O)$_2$(C_{1-4} alkyl)}, S(O)$_2$NR^{40}R^{41}, C(O)R^{42}, C(O)$_2$(C_{1-6} alkyl) (such as tert-butoxycarbonyl), C(O)$_2$(phenyl(C_{1-2} alkyl)) (such as benzyloxycarbonyl), C(O)NHR^{43}, S(O)$_2$R^{44}, NHS(O)$_2$NHR^{45}, NHC(O)R^{46}, NHC(O)NHR^{47} or NHS(O)$_2$R^{48}, provided none of these last four substituents is linked to a ring nitrogen;

k, l, p and q are, independently, 0, 1 or 2;

R^{20}, R^{22}, R^{24}, R^{26}, R^{27}, R^{29}, R^{31}, R^{33}, R^{37} and R^{40} are, independently, hydrogen or C_{1-6} alkyl;

R^{21}, R^{23}, R^{25}, R^{28}, R^{30}, R^{32}, R^{34}, R^{36}, R^{38}, R^{39}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, R^{47} and R^{48} are, independently, C_{1-6} alkyl (optionally substituted by halo, hydroxy, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl, C_{5-6} cycloalkenyl, S(C_{1-4} alkyl), S(O)(C_{1-4} alkyl), S(O)$_2$(C_{1-4} alkyl), heteroaryl, phenyl, heteroaryloxy or phenyloxy), C_{3-7} cycloalkyl, phenyl or heteroaryl; wherein any of the immediately foregoing phenyl and heteroaryl moieties are optionally substituted with halo, hydroxy, nitro, S(C_{1-4} alkyl), S(O)(C_{1-4} alkyl), S(O)$_2$(C_{1-4} alkyl), S(O)$_2$NH$_2$, S(O)$_2$NH(C_{1-4} alkyl), S(O)$_2$N(C_{1-4} alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, C(O)NH$_2$, C(O)NH(C_{1-4} alkyl), C(O)N(C_{1-4} alkyl)$_2$, CO$_2$H,

$CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3; and,

R^{21}, R^{23}, R^{25}, R^{28}, R^{30}, R^{34}, R^{35}, R^{36}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46} and R^{47} may additionally be hydrogen;

or a pharmaceutically acceptable salt thereof or a solvate thereof.

2. A process for preparing of a compound as claimed in claim 1 comprising:

3. A pharmaceutical composition which comprises a compound as claimed in claim1, or a pharmaceutically acceptable salt thereof or solvate thereof, and a pharmaceutically acceptable adjuvant, diluent or carrier.

4. A compound as claimed in claim1, or a pharmaceutically acceptable salt thereof or solvate thereof, for use as a medicament.

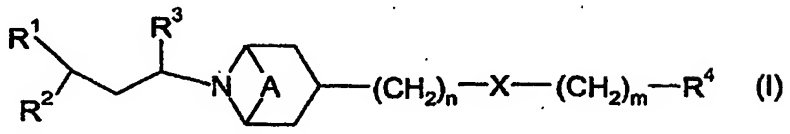
5. A compound as claimed in claim1, or a pharmaceutically acceptable salt thereof or solvate thereof, in the manufacture of a medicament for use in therapy.

6. A method of treating a CCR5 mediated disease state comprising administering to a patient in need of such treatment an effective amount of a compound as claimed in claim 1, or a pharmaceutically acceptable salt thereof or solvate thereof.

ABSTRACT

CHEMICAL COMPOUNDS

Compounds of formula (I):



(I)

wherein R^1, R^2, R^3, R^4, A, X, m and n are as defined; compositions comprising them, processes for preparing them and their use in medical therapy (for example modulating CCR5 receptor activity in a warm blooded animal).